



Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

4171 '01 MAY 14 A9 57

WAT
Villalba (550)
4/24/01
Be sure
that copy is
latter
to Mr. B...

13 April 2001

Mr. Gary J. Buehler
Director, Office of Generic Drugs (HFD-600)
Food and Drug Administration
Metro Park North 2, Room 286
7500 Standish Place
Rockville, Maryland 20855



SCF-036-C

Re: **NDA # 13-217/S-036 SKELAXIN (metaxalone) Tablets 400 mg**

Dear Mr. Buehler

NEW CORRESPONDENT

This letter is a follow-up to a submission made by Elan on February 27 2001 to the Office of Generic Drugs in which I provided you with a copy of data submitted to Dr. J. Bull (Attn. Dr. D. Bashaw) of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, CDER clearly demonstrating that comparable *in vitro* dissolution data alone were not sufficient to establish bioequivalence between different tablet formulations of metaxalone and the currently approved metaxalone formulation, SKELAXIN™. (See attachment 1).

Subsequent to this submission, we obtained a copy of a Citizen Petition filed on 6 March 2001 by Mutual Pharmaceutical Company of Philadelphia in which they submitted data together with the request to the FDA "to withhold approval of any abbreviated new drug application (ANDA) for a duplicate version of SKELAXIN® (Metaxalone) Tablets, 400 mg without an acceptable *in-vivo* fasting bioequivalence study demonstrating that the proposed test product and the reference product are bioequivalent".

01P-0117

ORIGINAL



LETI

For the reasons given in our February 27 submission and the March 6 Mutual Citizen Petition, Elan endorses Mutual's request. Metaxalone is a drug that presents a bioequivalence problem, and its entry in the Orange Book should reflect that fact.

Recently Elan has received notification from the Illinois Department of Public Health (March 22 2001, Attachment 2) as well as from the Drug Utilization Review Council of New Jersey Department of Health and Senior Services (April 11, 2001, Attachment 3) of an application by Zenith Goldline Pharmaceutical to include their "generic" version of metaxalone 400 mg on the respective state formularies.

Elan is very concerned about the activity of Zenith Goldline Pharmaceutical for the following reasons:

It is not our understanding that a Company may obtain inclusion of a prescription product in any state formulary before it has been approved for sale and distribution by the Food and Drug Administration;

In view of the data submitted to FDA by Mutual as well as by Elan, there is definitive scientific evidence that demonstrates that a comparative *in vitro* dissolution profile of a 400 mg metaxalone tablet compared to a 400 mg SKELAXIN™ tablet is a wholly invalid and inappropriate method for establishing bioequivalence between formulations of metaxalone. Therefore, even if the dissolution studies in the Zenith Goldline ANDA show

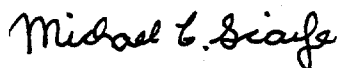
no differences in the formulations (you will note that they submitted *in vitro* dissolution data to the Illinois Department of Health), the studies are completely inadequate for purposes of demonstrating bioequivalence.

Elan has submitted evidence that metaxalone is too insoluble for dissolution studies to be predictive of *in vivo* bioavailability. Mutual has provided *in vivo* studies confirming this fact (equivalence *in vitro* but lack of equivalence *in vivo*) and demonstrating that in two attempts Mutual produced bioinequivalent formulations, as shown in blood level studies. These data mean that, as a scientific matter, all ANDAs for metaxalone must contain *in vivo* bioequivalence data.

I would be grateful if you could therefore confirm to Elan the current status of OGD classification for metaxalone 400 mg as requiring *in vivo* bioequivalence data and I respectfully request that you inform Zenith Goldline Pharmaceutical that their submissions to state formulary authorities are scientifically inappropriate and premature.

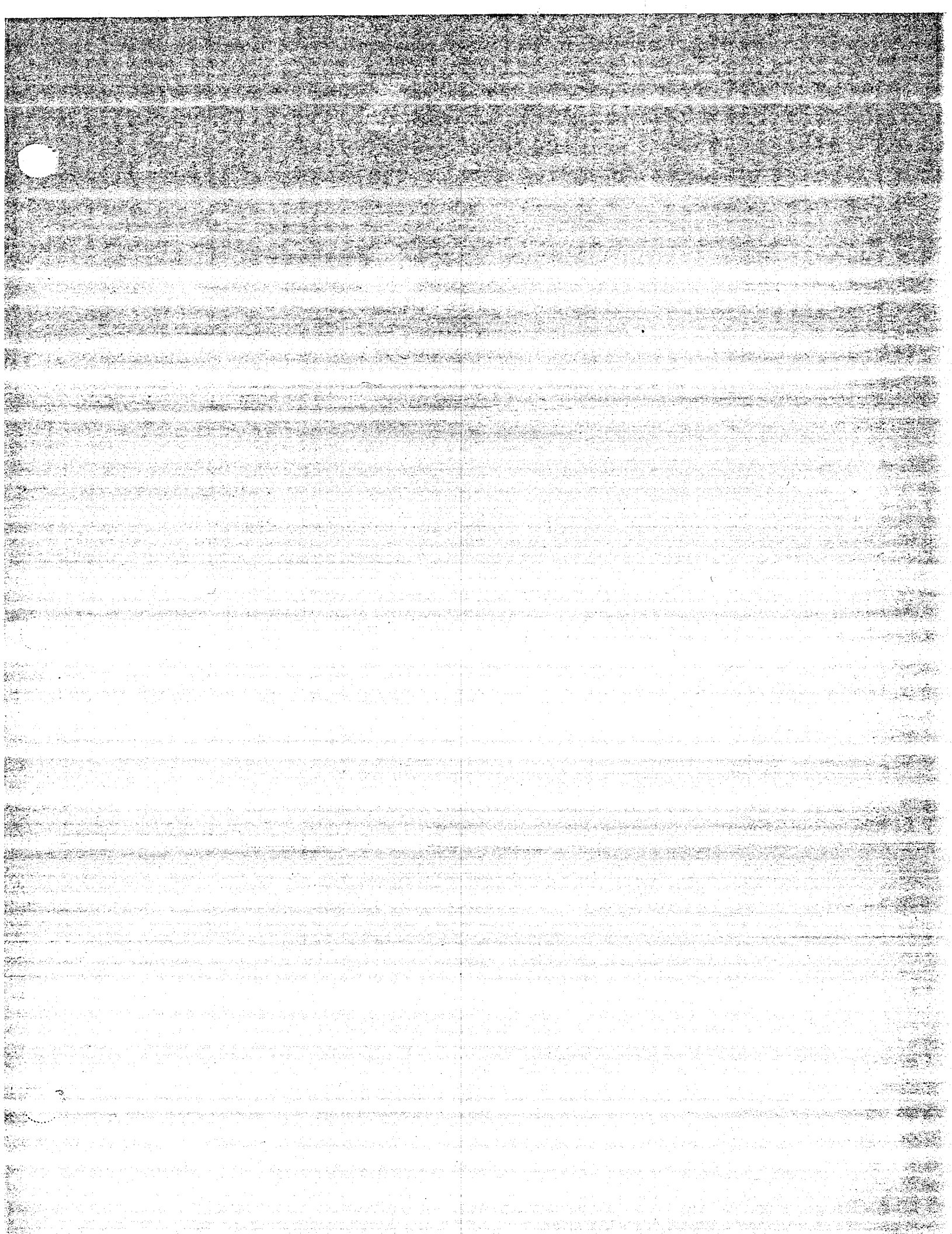
I am at your disposal for further information or clarification. My direct phone number is; 650-553-7187; fax: 650-616-2650.

Yours sincerely,



Michael C. Scaife, Ph.D.

Vice President, Regulatory Affairs,
Elan Pharmaceuticals and Carrick Laboratories





Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

February 27 2001

Garry Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard HFD-550
Rockville, MD 20857-1706

Re: **NDA # 13-217/S-036 SKELAXIN (metaxolone) Tablets 400 mg**

Dear Dr. Buehler

This communication is to inform the Office of Generic Drugs of data that we, as the Innovator Company wish to share with you for a product marketed under the name of SKELAXIN* (active ingredient, metaxolone).

For your background information, please be aware that SKELAXIN* was the subject of DESI Notice 9947 for metaxolone and that in the Federal Register 39, No. 159 dated August 15 1974, the then Commissioner concluded that the efficacy of metaxolone had been demonstrated.

I am enclosing copies of correspondence (dated February 27 2001) and supportive data that I have recently submitted to Dr. Jonca Bull of the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug products, CDER

In view of the fact that this product is eligible for ANDA submissions, Elan feels that it is important that we urgently bring to your attention the attached information which in summary demonstrates the following:

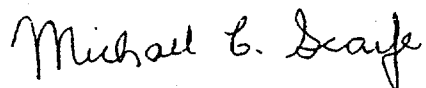
- Metaxolone, according to the FDA Guidance Document on eligibility for "Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System" is a low solubility drug and as such is **not** eligible for a waiver as detailed within 21 CFR 320.22.;
- Preliminary but convincing data comparing the *in vitro* dissolution profiles of two tablet formulations of metaxolone and SKELAXIN* to *in vivo* data generated in human volunteers has shown that an equivalent dissolution profile for metaxolone tablets is **not** a scientifically valid substitution for a bioequivalence assessment.

This was in fact the conclusion reached by Dr. Bull's Division in a letter sent to our sister Company Carrick Laboratories (letter dated April 14 2000) which is included for your information). In the light of the data outlined above, Elan has agreed with the Division to provide more definitive data both on the *in vitro* dissolution profile for SKELAXIN* tablets as well as to provide a pharmacokinetic profile, both then serving to provide the Agency with a standard against which potential ANDA Applications should be evaluated.

As we generate additional data, I will continue to send copies to the Office of Generic Drugs for your evaluation and comment.

Please feel free to contact me at (650) 553-7187 if you require further information or clarification at this stage.

Sincerely,

A handwritten signature in cursive script that reads "Michael C. Scaife".

Michael C. Scaife, Ph.D.,
Vice President, Regulatory Affairs



Elan Pharmaceuticals

800 Gateway Boulevard
South San Francisco, CA 94080
Telephone (650) 877-0900
Fax (650) 877-8370

February 27 2001

Jonca Bull, MD
Acting Director, Division of Anti-Inflammatory, Analgesic
And Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room
9201 Corporate Boulevard HFD-550
Rockville, MD 20857

Re: NDA # 13-217/S-036 SKELAXIN (metaxolone) Tablets 400 mg

Dear Dr. Bull,

This communication is a follow-on to our letter of February 16 2001 in which we stated that we would be providing the Agency with data that was the basis for our conclusion that there is no correlation between the *in vitro* dissolution profile of metaxolone tablet preparations and their corresponding *in vivo* pharmacokinetic profiles.

In the first document, "Determination of the drug substance equilibrium solubility classification of metaxolone under physiological pH conditions"; we provide data on the equilibrium aqueous solubility of metaxolone, the active ingredient in SKELAXIN* as determined according to the FDA Guidance document entitled "Waiver of *in vivo* bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a Biopharmaceutics Classification System" (August 2000). The results of this study clearly demonstrate that metaxolone is classified as a low solubility drug.

In the second document, "Bioavailability of metaxolone formulations as assessed by *in vitro* dissolution compared to *in vivo* pharmacokinetic profiles" we provide the results of our preliminary investigation into the *in vitro* dissolution profiles of two different tablet formulations of metaxolone compared to SKELAXIN*, together with their corresponding *in vivo* pharmacokinetic profiles.

The results clearly show that there is not a correlation between the *in vitro* dissolution profile of different tablet formulations of metaxolone and the *in vivo* pharmacokinetic profile.

It was based upon the findings from these two investigations that we have concurred with the Agency that it is important for ourselves, as the originator Company of SKELAXIN* to adequately define the *in vivo* pharmacokinetic profile for the product as well as to provide to the Agency, a more detailed *in vitro* dissolution profile for the tablet presentation that more clearly defines the product. Further supportive data to this effect will be provided for the Agency's review in the near future.

Please feel free to contact me at (650) 553-7187 if you require further information or clarification at this stage.

Sincerely,

Michael C. Scaife

Michael C. Scaife, Ph.D.,
Vice President, Regulatory Affairs

Desk Copies:

E. Dennis Bashaw, Pharm.D.,
Sharon Schmidt, MS



**elan
pharmaceutical
technologies**

**3000 Horizon Drive
King of Prussia, PA 19406**

Study Report No: SR-N1257-0001.00

Period Covered: 13Feb-2001 to 016-Feb-2001

**Determination Of The Drug Substance Equilibrium Solubility Classification
Of Metaxalone Under Physiological pH Conditions**

26-Feb-2001

Contributors: S. Wheeler, R. Patel, J. Strasters, J. Bullock

APPROVAL PAGE

Written by: _____ Date: _____

John Bullock
Assistant Director, Analytical Sciences Department

Reviewed by: _____ Date: _____

Shirley Wheeler
Associate , Analytical Sciences Department

Approved by: _____ Date: _____

Jon Swanson
Director, Analytical Sciences & GMP Operations

ABSTRACT

The Analytical Sciences Department Of Elan Pharmaceutical Technologies was requested to determine the equilibrium aqueous solubility of Metaxalone, the active pharmaceutical ingredient (API) in Skelaxin® Tablets, under physiological pH conditions. The objective of this study was to determine the solubility classification of Metaxalone as it relates to the Biopharmaceutical Classification System (BCS). Equilibrium solubility of Metaxalone was determined at 37 °C in a series of pH/buffer media spanning the range from pH 1 to pH 7.4. The solubility of Metaxalone was found to be fairly constant over this pH range averaging about 0.36 mg/mL. Based on the solubility of Metaxalone and considering the highest dose strength (400mg) for Skelaxin® Tablets, Metaxalone is classified as a low solubility API based on the BCS system.

Table of Contents

ABSTRACT 3

TABLE OF CONTENTS 4

INDEX OF TABLES 4

INDEX OF FIGURES 5

1. INTRODUCTION/STUDY OBJECTIVES 6

2. EXPERIMENTAL 7

 2.1. BATCH DESCRIPTION FOR BULK METAXALONE API 7

 Technical Information 7

 2.2. INSTRUMENTATION 7

 2.3. BUFFER MEDIA PREPARATIONS 7

 2.4. SOLUBILITY DETERMINATION PROTOCOL 8

 2.5. UV CONCENTRATION TEST METHOD 8

 2.5.1. Instrumental: 8

 2.5.2. Standard Preparations: 8

 2.5.3. Analysis Procedure: 9

 2.5.4. Calculations: 9

3. DATA/RESULTS 9

 3.1. METAXALONE UV CALIBRATION RESULTS 9

 3.2. METAXALONE EQUILIBRIUM SOLUBILITY RESULTS 11

4. DISCUSSION 12

5. CONCLUSION 13

6. REFERENCES 13

7. ATTACHMENTS 13

 Attachment 1: Carrick Laboratories, Inc. Analytical Method No. S-28-C 14

 Attachment 2: Roche Certificate of analysis Metaxalone batch MH00095074 15

Index of Tables

Table 1 Summary of Linear Regression Results For The Metaxalone UV Response at 280nm 10

Table 2 Summary Of Metaxalone Equilibrium Aqueous Solubility Data At 37 °C Between pH 1 And pH 7.4 11

Index of Figures

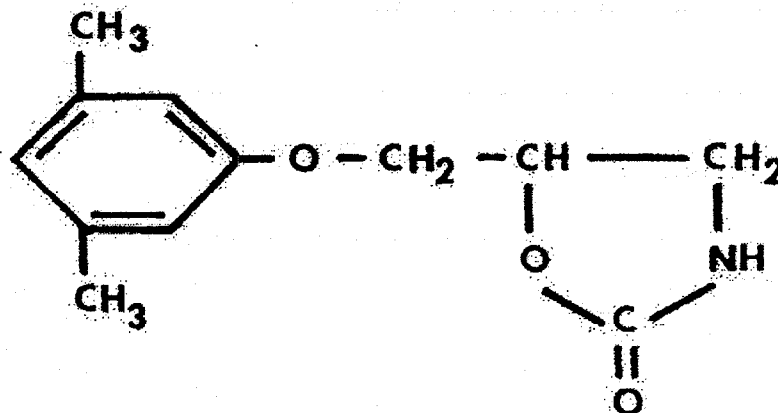
Figure 1 Structure Of Metaxalone	7
Figure 2 Typical Metaxalone Standard Calibration Curve (T = 16.5 Hours)	10
Figure 3 Solubility Profiles of Metaxalone At 37 °C As A Function Of Time In Aqueous Media Ranging From pH 1 To pH 7.4	12

1. Introduction/Study Objectives

The Analytical Sciences Department of Elan Pharmaceutical Technologies (EPT) was requested to determine the equilibrium aqueous solubility of Metaxalone, the active pharmaceutical ingredient (API) in Skelaxin® Tablets, under physiological pH conditions. The objective of this study was to determine the solubility classification of Metaxalone as it relates to the Biopharmaceutical Classification System (BCS). The BCS system is used to classify an API based on its aqueous solubility and intestinal permeability properties. This study was focused only on evaluating the aqueous solubility properties of Metaxalone. This was performed at 37 °C in a series of pH/buffer media spanning the pH range from pH 1 to pH 7.4.

The equilibrium aqueous solubility characteristics of Metaxalone were determined using the FDA Guidance Document entitled "Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" (August 2000) as a guideline. For expediency, a modification was made to the experimental procedure recommended in Section III, subpart A of this FDA guidance. This entailed the use of an ultra-violet spectrophotometric (UV) method in place of a stability-indicating HPLC method for the concentration determination of Metaxalone in the various media. The UV method was adapted from Carrick Laboratories, Inc. Analytical Method No. S-28-C (Attachment 1) for the dissolution testing of Skelaxin® Tablets.

Solubility determinations were conducted in a total of six media including water, 0.1 M HCl, USP simulated gastric fluid without enzymes (SGF), and aqueous buffers at pH 3.0, 6.8 and 7.4. The FDA guidance states that the number of pH conditions required to accurately define the pH-solubility profile should be based on the ionization characteristics of the API. The structure of Metaxalone provided in Figure 1 reveals that there are no ionizable functional groups for the compound. Thus, the selected pH conditions for this study should adequately characterize the pH-solubility profile of this API. All solubility experiments for this study were conducted at 37 °C with solubility determinations made over the course of 25 hours.

Figure 1 Structure Of Metaxalone

2. *Experimental*

2.1. Batch Description For Bulk Metaxalone API

Technical Information
(refer to Attachment 2 for Certificate of analysis)

- 2.1.1. Supplier: Roche
- 2.1.2. Batch No.: MH00095074
- 2.1.3. Expiry Date: 29-Aug-2005
- 2.1.4. Assay by HPLC (dried substance): 99.6%
- 2.1.5. Sum of Impurities: 0.1%

2.2. Instrumentation

- 2.2.1. pH meter: Beckman Model 660
- 2.2.2. UV Spectrophotometer: HP Model 8453 Diode-array UV/Vis
- 2.2.3. Dissolution Apparatus: Distek Model 5100 Dissolution Apparatus

2.3. Buffer Media Preparations

The following media were prepared for conducting the solubility experiments.

- 2.3.1 **Water:** USP Purified Water
- 2.3.2 **0.1 M HCL:** For each liter of 0.1M HCL, add 8.3 mL of concentrated HCL to 200 mL of water. Dilute to 1000 mL with water and mix well.

- 2.3.3 **Potassium Phosphate 0.2 M:** Dissolve 27.22 g of potassium phosphate monobasic (KH_2PO_4) in water, and dilute with water to 1000 mL.
- 2.3.4 **pH 6.8 Buffer (Potassium Phosphate):** Place 250 mL of 0.2 M Potassium phosphate into an appropriate container. Add 112 mL of 0.2 M NaOH. Then add water to 1000 mL. Mix well. Adjust pH if necessary to 6.8 ± 0.05 with 0.2 M NaOH or 0.2 N Phosphoric acid.
- 2.3.5 **pH 7.4 Buffer (Potassium Phosphate):** Place 250 mL of 0.2 M Potassium phosphate into an appropriate container. Add 196 mL of 0.2 M NaOH. Then add water to 1000 mL. Mix well. Adjust pH if necessary to 7.4 ± 0.05 with 0.2 M NaOH or 0.2 N Phosphoric acid.
- 2.3.6 **pH 3.0 Buffer (Potassium Phosphate):** Place 250 mL of 0.2 M Potassium phosphate into an appropriate container. Add about 600 mL of water. Adjust pH to 3.0 with 0.2 N Phosphoric acid. Add water to 100mL.
- 2.3.7 **Simulated Gastric Fluid (USP):** Dissolve 2.0 g sodium chloride and 7.0 mL of concentrated HCL and sufficient water to make 1000 mL.

2.4. Solubility Determination Protocol

Equilibrium solubility experiments were conducted at 37 °C using a dissolution apparatus equipped with paddles conforming to USP apparatus 2 specifications.

- 2.4.1. Add about 5g of Metaxalone API to 500mL of the aqueous buffer contained in a dissolution vessel equilibrated at 37°C.
- 2.4.2. Start a timer and stir solutions at 150rpm.
- 2.4.3. At selected time points (1, 2, 16.5 and 25 hours) withdraw a 10mL aliquot and filter through a 0.45 micron nylon syringe filter (Gelman 0.45 micron 25mm Acrodisc)
- 2.4.4. Quantitatively dilute 2.0mL of the filtrate to 10mL with methanol and mix well.

2.5. UV Concentration Test Method

The following is an outline of the UV procedure used to determine the Metaxalone concentration in the various aqueous media.

2.5.1. Instrumental:

Wavelength: 280nm
Pathlength: 1cm
Diluent: 80% methanol/water

2.5.2. Standard Preparations:

Standard 1: Weigh about 25mg of Metaxalone API into a 250mL volumetric flask. Dissolve with diluent with shaking and/or sonication and dilute to volume. Nominal concentration is 0.1mg/mL

Standard 2: Dilute 10mL of Standard 1 to 25mL with diluent.
Nominal concentration is 0.04mg/mL

Standard 3: Dilute 5mL of Standard 1 to 25mL with diluent. Nominal
concentration is 0.02mg/mL

Standard 4: Dilute 2mL of Standard 1 to 25mL with diluent. Nominal
concentration is 0.008mg/mL

Standard 5: Dilute 1mL of Standard 1 to 25mL with diluent. Nominal
concentration is 0.004mg/mL

2.5.3. Analysis Procedure:

- 2.5.3.1. Blank the UV with diluent at 280nm
- 2.5.3.2. Measure the absorbance of Standards 1-5 at 280nm in
triplicate and construct a standard curve.
- 2.5.3.3. Measure the absorbance of the sample preparations at
280nm in triplicate.

2.5.4. Calculations:

Calculate the solubility of Metaxalone in the medium using the following formula:

$$\text{Solubility in mg/mL} = (A_{\text{sm}} - Y_{\text{int}}) / m \times \text{DF}$$

A_{sm} = Absorbance of sample at 280nm

Y_{int} = Y-intercept from the standard curve

m = Slope from the standard curve

DF = Sample dilution factor (10/2 = 5)

3. Data/Results

3.1. Metaxalone UV Calibration Results

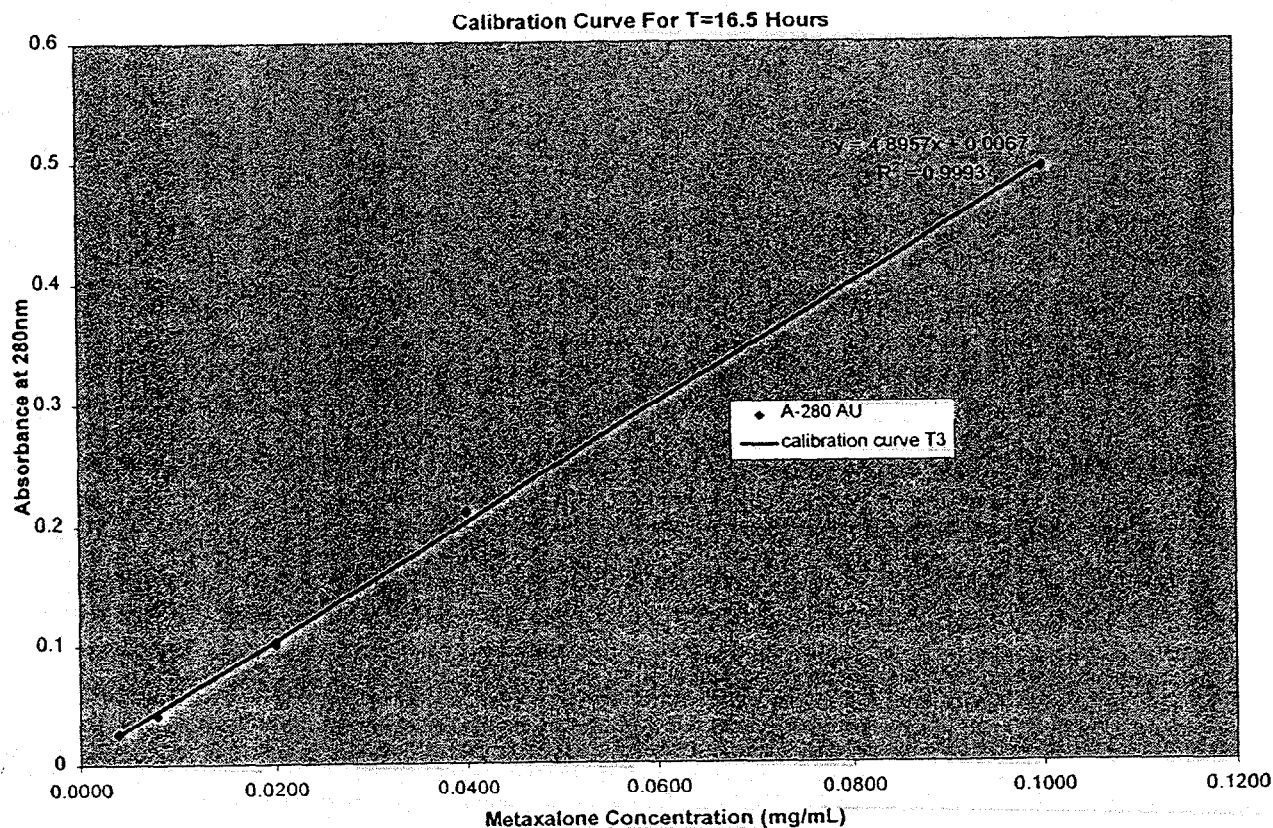
Metaxalone standard UV calibration curves were generated for each of the sampling time points used to determine the Metaxalone solubility for this study (1, 2, 16.5 and 25 hours). In general, the absorbance at 280nm was linear throughout the standard concentration range of 0.004mg/mL to 0.1mg/mL. However, for the first calibration conducted at the one hour time point there was a small amount of curvature at the high end of the concentration range. Therefore, for the one hour time point a second order polynomial fit of the Metaxalone standard data was used. For all of the other standard

curves, a linear fit was used. Table 1 summarizes the regression results for the various standard curves and Figure 2 contains a typical Metaxalone standard response curve using a linear model. The absorbance values for all solubility test samples in the various media were within the range of this standard curve.

Table 1 Summary of Linear Regression Results For The Metaxalone UV Response at 280nm

Regression Parameter	Calibration Curve			
	T=1 Hour	T=2 Hour	T=16.5 Hour	T=25 Hour
Y-intercept	-0.00903645	0.006104059	0.006665466	0.00970774
X Variable 1 (slope)	7.190959883	4.961573338	4.895655356	4.82532193
X Variable 2	-19.7814713	NA	NA	NA
Multiple R	0.999964426	0.999737996	0.999674654	0.999675838
R-Square	0.999928854	0.99947606	0.999349414	0.999351782
Adjusted R-Square	0.999916996	0.999435757	0.999299369	0.999301919
Standard Error	0.001691558	0.004291017	0.004718359	0.004642096
Observations	15	15	15	15

Figure 2 Typical Metaxalone Standard Calibration Curve (T = 16.5 Hours)



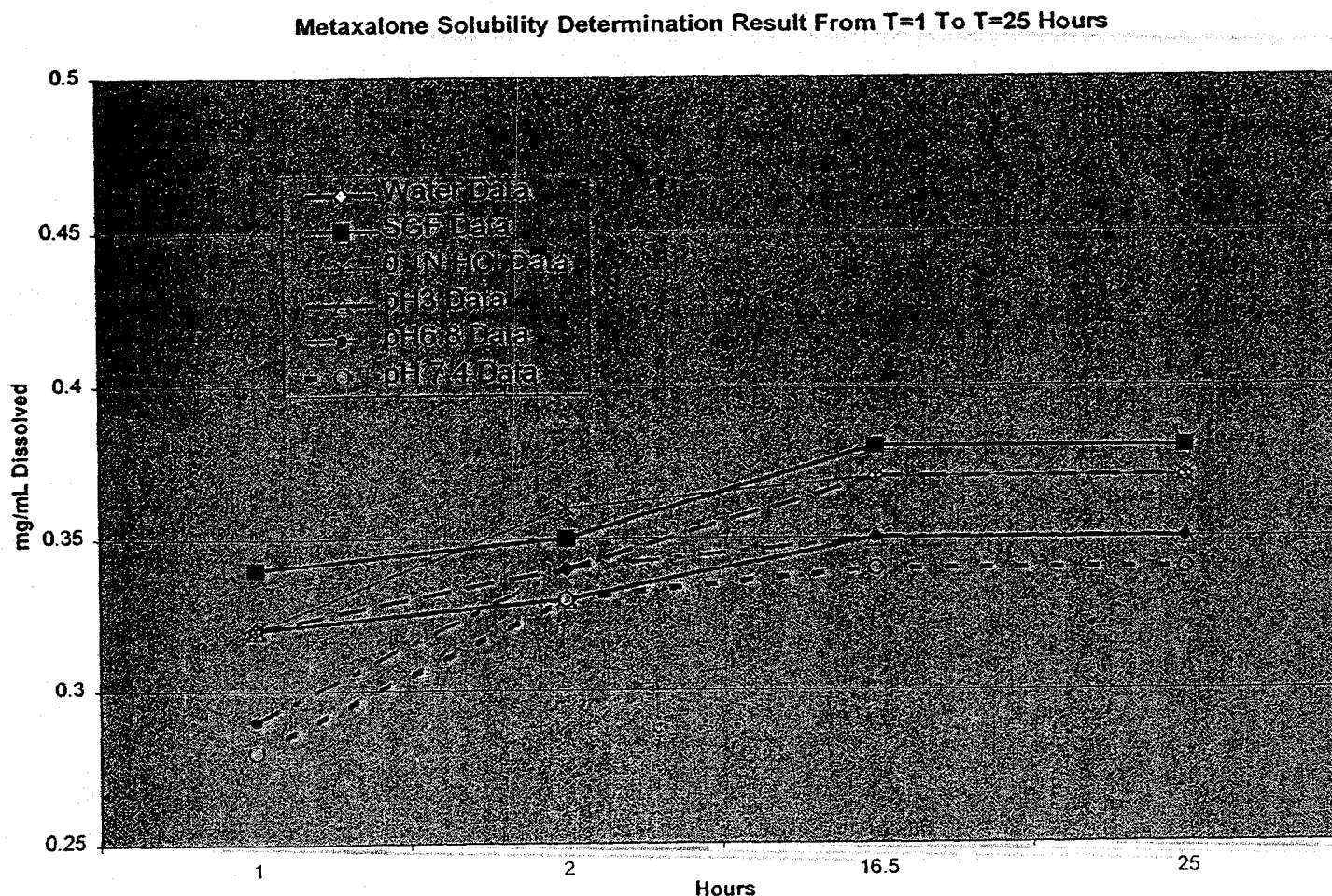
3.2. Metaxalone Equilibrium Solubility Results

Table 2 and Figure 3 summarize the solubility data collected for Metaxalone in the various aqueous media over the course of 25 hours. The consistency in the results between the 16.5 hour point and 25 hour point in all media supports that equilibrium solubility at 37 °C was achieved in all six media. Based on the structure of Metaxalone and the absence of any ionizable functional groups on the molecule, no significant pH dependence in the solubility data was anticipated. This is supported by the data at the 25 hour time point which shows the solubility ranging from 0.34mg/mL to 0.38mg/mL in the different media. The small differences (0.04mg/mL maximum) can be attributed to ionic strength or surface tension differences for the various media. The results obtained in the phosphate buffers at three different pH values were between 0.34-0.35mg/mL. The results obtained in the two acidic media (0.1M HCl and SGF) were 0.37-0.38 mg/mL while in water the result was 0.37mg/mL.

Table 2 Summary Of Metaxalone Equilibrium Aqueous Solubility Data At 37 °C Between pH 1 And pH 7.4

		Solubility Experiment Time In Hours							
		T=1		T=2		T=16.5		T=24	
		Replicate	Avg.	Replicate	Avg.	Replicate	Avg.	Replicate	Avg.
Medium		mg/mL	mg/mL	mg/mL	mg/mL	mg/mL	mg/mL	mg/mL	mg/mL
Water	1	0.3246	0.32	0.3408	0.34	0.3676	0.37	0.3698	0.37
	2	0.3155		0.3407		0.3713		0.3736	
	3	0.3158		0.3404		0.3714		0.3736	
SGF	1	0.3361	0.34	0.3543	0.35	0.3737	0.38	0.3760	0.38
	2	0.3356		0.3524		0.3768		0.3791	
	3	0.3361		0.3536		0.3803		0.3827	
0.1M HCl	1	0.3118	0.32	0.3570	0.36	0.3687	0.37	0.3709	0.37
	2	0.3166		0.3565		0.3719		0.3742	
	3	0.3172		0.3592		0.3717		0.3740	
pH 3.0	1	0.3137	0.32	0.3335	0.33	0.3470	0.35	0.3489	0.35
	2	0.3175		0.3344		0.3465		0.3484	
	3	0.3191		0.3350		0.3466		0.3485	
pH 6.8	1	0.2925	0.29	0.3406	0.34	0.3510	0.35	0.3530	0.35
	2	0.2939		0.3402		0.3543		0.3563	
	3	0.2939		0.3401		0.3536		0.3556	
pH 7.4	1	0.2761	0.28	0.3297	0.33	0.3369	0.34	0.3386	0.34
	2	0.2785		0.3302		0.3392		0.3410	
	3	0.2789		0.3306		0.3395		0.3413	
Equilibrium Solubility (T=25 Hours) Average For All Media									0.36

Figure 3 Solubility Profiles of Metaxalone At 37 °C As A Function Of Time In Aqueous Media Ranging From pH 1 To pH 7.4



4. Discussion

The results from this study have confirmed the anticipated lack of a pH dependence of the aqueous solubility of Metaxalone under physiological pH conditions. Within the range of pH 1 to pH 7.4 the average solubility determined for Metaxalone was 0.36mg/mL with a range of 0.34mg/mL to 0.38mg/mL.

In order to determine the solubility classification of Metaxalone according to the BCS system, it is necessary to calculate the volume of aqueous medium sufficient to dissolve the highest dose strength of the drug within the pH range of pH 1 to pH 7.5. To be classified as highly soluble, the highest dose strength must be soluble in ≤ 250 mL of

aqueous medium. For Skelaxin® Tablets with a dose strength of 400mg per tablet this equates to a solubility of at least 1.6mg/mL (400mg/250mL) to be considered a highly soluble drug. The highest solubility value that was determined in this pH range for Metaxalone was 0.38mg/mL. Therefore, according to the BCS classification system, Metaxalone is considered a low solubility drug.

5. Conclusion

The equilibrium solubility of Metaxalone API was evaluated at 37 °C in aqueous media spanning the range from pH 1 to pH 7.4. The following conclusions can be drawn from this study:

- There is no significant pH dependence to the aqueous solubility of Metaxalone under physiological pH conditions (pH 1 to pH 7.4)
- The average solubility of Metaxalone in this pH range is 0.36mg/mL.
- Considering the aqueous solubility of Metaxalone and the highest dose strength of the Skelaxin® drug product, Metaxalone is classified as a low solubility drug.

6. References

- 6.1. Laboratory notebook: WHR-5749-159
- 6.2. Laboratory notebook: JKS-5771-008

7. Attachments

- 7.1. Attachment 1: Carrick Laboratories, Inc. Analytical Method No. S-28-C
- 7.2. Attachment 2: Roche Certificate of analysis Metaxalone batch MH00095074

Attachment 1: Carnrick Laboratories, Inc. Analytical Method No. S-28-C

26-Feb-2001

elan pharmaceutical technologies, Confidential

Attachment 2: Roche Certificate of analysis Metaxalone batch MH00095074

26-Feb-2001

elan pharmaceutical technologies, Confidential

Bioavailability of metaxalone formulations as assessed by *in vitro* dissolution compared to *in vivo* pharmacokinetic profiles.

Executive Summary

Pharmaceutical equivalents of poorly soluble drugs, such as metaxalone, and/or slowly dissolving immediate release (IR) solid dosage forms, such as Skelaxin, have potential bioequivalence problems which may be due to differences in drug dissolution in-vivo. In the absence of a validated *in vivo* / *in vitro* correlation, comparability of *in-vitro* dissolution profiles does not indicate *in-vivo* bioequivalence for such products.

Two studies undertaken to assess the *in-vivo* performance of pharmaceutical equivalents to Skelaxin confirmed the lack of predictability of *in-vitro* dissolution for *in-vivo* bioavailability for metaxalone formulations. The first study evaluated a tablet formulation (BB5800040) that released faster *in-vitro* than Skelaxin, using a standard dissolution test for a formulation of a poorly soluble drug (water with SLS, USP II@75rpm), but had significantly reduced bioavailability compared to Skelaxin. The second study evaluated a tablet formulation (BB5800047) that had a slightly slower dissolution than Skelaxin at a couple of timepoints, using the same standard dissolution method, but had greatly enhanced bioavailability compared to Skelaxin. Dissolution of these same formulations using lower agitation and less surfactant found that the first formulation (BB5800040) was slower *in-vitro* to Skelaxin, somewhat reflecting *in-vivo* performance, but the second formulation (BB5800047), which showed greatly enhanced bioavailability compared to Skelaxin *in-vivo*, was similar in terms of *in-vitro* performance to Skelaxin.

These data therefore confirm the lack of predictability of *in-vitro* dissolution for potential *in-vivo* bioavailability and bioequivalence problems with formulations of metaxalone and provides compelling evidence that *in-vitro* dissolution cannot be used as a surrogate for *in-vivo* performance of pharmaceutical equivalents of Skelaxin.

Bioavailability of metaxalone tablet formulations as assessed by in vitro dissolution compared to in vivo pharmacokinetic profiles.

Background

Metaxalone is a poorly soluble drug (highest dose strength (400mg) not soluble in 250ml aqueous media) and Skelaxin is a slowly dissolving IR solid oral dosage form (<85% dissolved in 30 minutes). Pharmaceutical equivalents of poorly soluble drug products and/or slowly dissolving IR products have potential bioequivalence problems which may be due to differences in drug dissolution in-vivo. In the absence of a validated in vivo / in vitro correlation, comparability of in-vitro dissolution profiles does not indicate in-vivo bioequivalence for such products.

In-vitro and in-vivo evaluation of Skelaxin and pharmaceutical equivalents.

Two studies (summarised below) were undertaken to assess the in-vivo performance of pharmaceutical equivalents to Skelaxin. The dissolution method for release of these formulations was paddles (USP II) at 75rpm, using 1000ml water with 2% SLS, in order to ensure sink conditions.

Study PP99-466

Study Design

This study was a two-treatment, two-period crossover study undertaken in 36 healthy volunteers (38 enrolled, 36 completed). A single oral 400mg tablet dose of metaxalone (Lot # BB5800040) or Skelaxin (Lot # GS639A) was administered in a randomised manner in each treatment period. There was a 7-day washout between treatments. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 30, 36 and 48 hours after dosing.

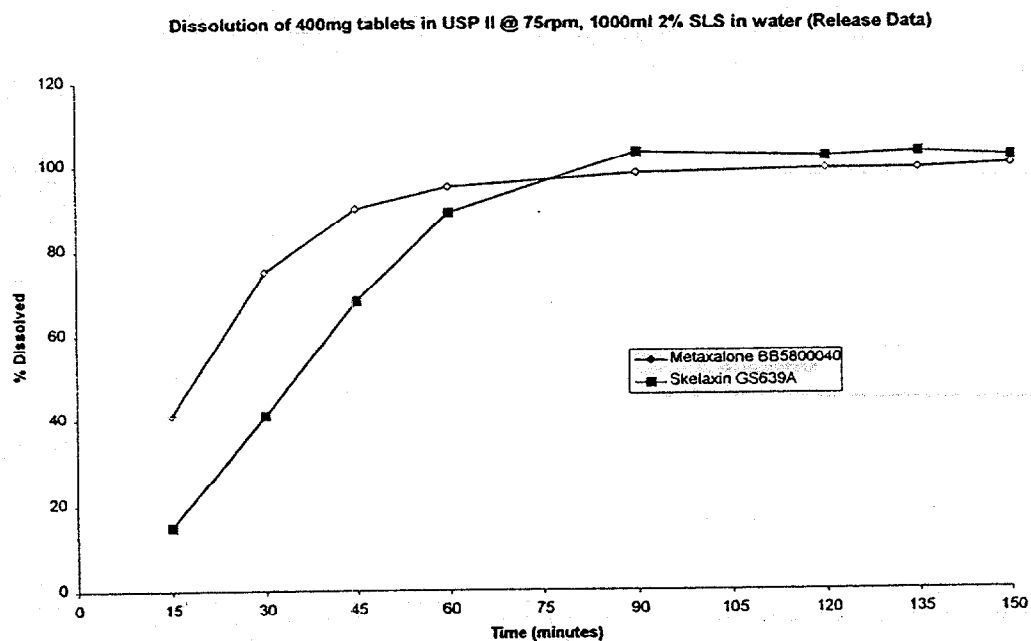
In-vitro dissolution

The In-vitro dissolution test for release was performed on twelve tablets of metaxalone (Lot # BB5800040) and Skelaxin (Lot # GS639A) using USP II (paddles) at 75rpm. 1000ml of an aqueous media containing 2% SLS was used to ensure the achievement of sink conditions. Samples were analysed at 15, 30, 45, 60, 90, 120, 135 and 150 minutes. Both products were similar in terms of potency (metaxalone Lot # BB5800040 : 102.3% ; Skelaxin Lot # GS639A : 99.6%). The dissolution of the test product (BB5800040) was faster than the dissolution of the reference product (Lot # GS639A) at 15, 30, 45 and 60 minutes (Table 1, Figure 1).

Table 1
Dissolution of 400mg tablets in USP II @ 75rpm, 1000ml 2% SLS in water
(Release Data)

Time Minutes	Metaxalone BB5800040			Skelaxin GS639A		
	% Diss.	% CV	Range	% Diss	% CV	Range
15	41	35	20-62	15	6	13-17
30	75	23	48-91	41	4	38-44
45	90	9	75-96	68	5	63-73
60	95	3	90-98	89	3	85-95
90	98	1	96-100	103	4	98-114
120	99	1	97-101	102	1	98-104
135	99	2	97-102	103	2	97-106
150	100	2	97-102	102	2	97-104

Figure 1



In-vivo performance

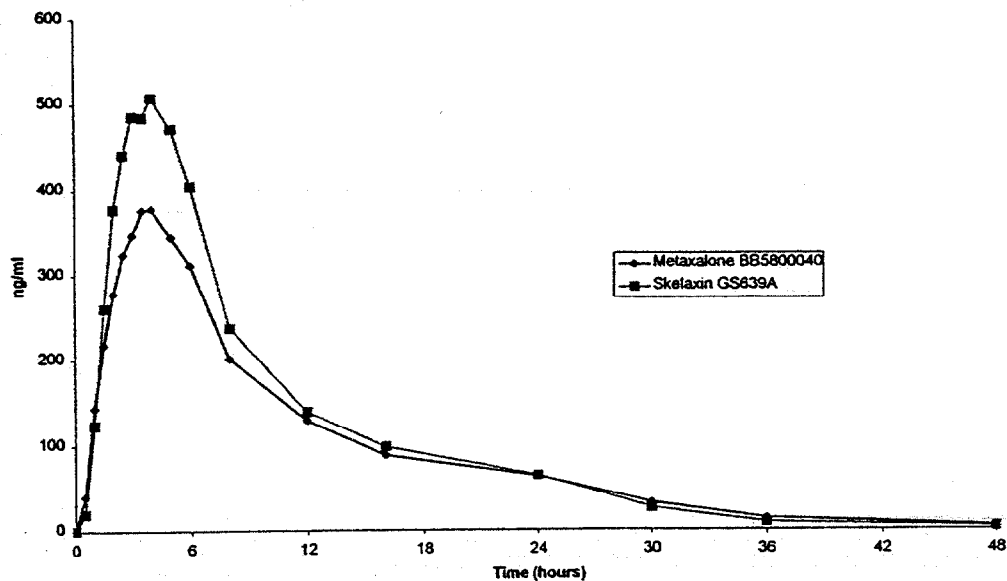
Thirty-five of the thirty-six subjects completing the study are included in the analysis. Subject 10 was not included in the analysis as there was analytical interference in both the original and reanalysed data for this subject. In contrast to the faster dissolution of metaxalone Lot # BB5800040 compared to Skelaxin Lot # GS639A, using the referenced dissolution method for release, the C_{max} and AUC of this metaxalone formulation were significantly lower than that for Skelaxin (Table 2, Figure 2).

Table 2
Pharmacokinetic Parameters – PP99-466

Parameter	Metaxalone BB5800040 Mean (CV%)	Skelaxin GS639A Mean (CV%)	Ratio		
			Mean	% CV	Range
C _{max} (Ln)C _{max} 90% CI	518 (59) 425 56-85	669 (39) 620	84	68	14-285
AUC (Ln)AUC _t 90%CI	4365 (48) 3932 75-90	5215 (35) 4784	86	30	37-135
AUC _{inf} (Ln)AUC _{inf} 90% CI	4569 (44) 4196 77-93	5074 (34) 4939	89	32	37-158
T _{max}	4	3			
T _{1/2}	8	7			

Figure 2

Plasma Concentrations – PP99-466



Summary

The in-vitro dissolution of metaxalone Lot # BB5800040, a pharmaceutically equivalent formulation to Skelaxin was faster than the in-vitro dissolution of Skelaxin Lot # GS639A using the dissolution method for release. However, the in-vivo evaluation found metaxalone Lot # BB5800040 to have a lower C_{max} and AUC than Skelaxin Lot # GS639A. Therefore the in-vitro dissolution using the dissolution method for release was not predictive of in-vivo performance for the pharmaceutical equivalents evaluated in this study.

Study PP99-642

Study Design

This study was a two-treatment, two-period crossover study undertaken in 46 healthy volunteers (48 enrolled, 46 completed). A single oral 400mg dose of metaxalone (Lot # BB5800047) or Skelaxin (Lot # GS639A) was administered in a randomised manner in each treatment period. There was a 14-day washout between treatments. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36 and 48 hours after dosing.

In-vitro dissolution

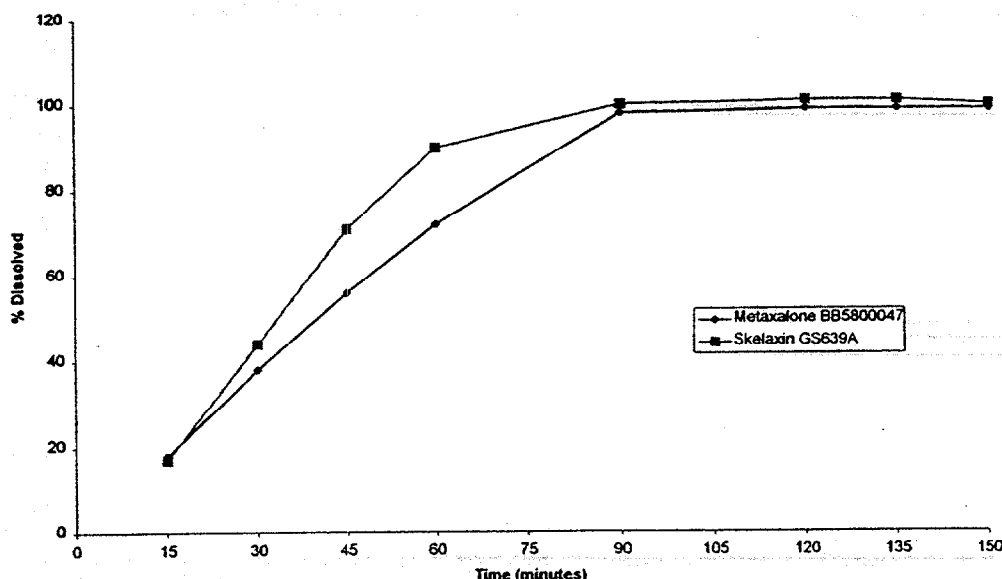
The In-vitro dissolution test for release was performed on twelve units of metaxalone (Lot # BB5800047) and Skelaxin (Lot # GS639A) using USP II (paddles) at 75rpm. 1000ml of an aqueous media containing 2% SLS was used to ensure the achievement of sink conditions. Samples were analysed at 15, 30, 45, 60, 90, 120, 135 and 150 minutes. Both products were similar in terms of potency (metaxalone Lot # BB5800047 : 100% ; Skelaxin Lot # GS639A : 99.9%). The dissolution of the test product (BB5800047) was slightly slower than the dissolution of the reference product (Lot # GS639A) at 45 and 60 minutes (Table 3, Figure 3).

Table 3
Dissolution of 400mg tablets in USP II @ 75rpm, 1000ml 2% SLS in water
(Release Data)

Time Minutes	Metaxalone BB5800047			Skelaxin GS639A		
	% Diss.	% CV	Range	% Diss	% CV	Range
15	18	6	17-21	17	7	15-18
30	38	4	35-40	44	4	41-47
45	56	4	52-60	71	4	67-78
60	72	5	65-78	90	2	87-94
90	98	1	95-99	100	1	98-101
120	99	1	97-100	101	1	99-102
135	99	1	98-100	101	1	99-103
150	99	1	97-99	100	1	99-101

Figure 3

Dissolution of 400mg tablets in USP II @ 75rpm, 1000ml 2% SLS in water (Release Data)



In-vivo performance

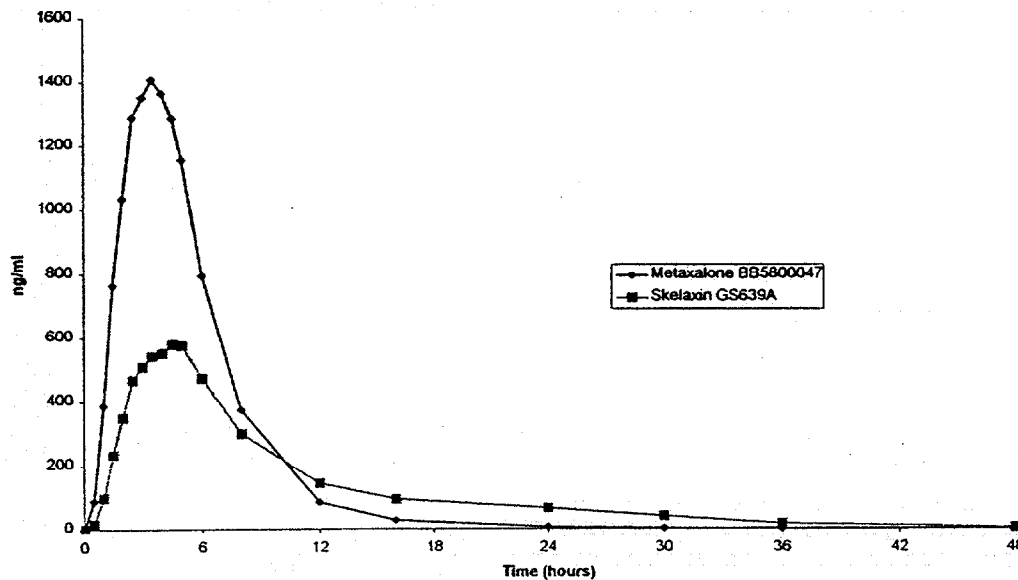
Twenty-four of the forty-six subjects completing the study are included in the analysis. Samples from only 30 subjects were analysed on the sponsor's request. Data for subjects 5-8 are not included in the analysis due to poor chromatography and interference and the bioanalysis for subjects 27 and 28 was stopped due to a retention time shift. In contrast to the slightly slower dissolution of metaxalone Lot # BB5800047 compared to Skelaxin Lot # GS639A, using the referenced dissolution method for release, the Cmax and AUC of this metaxalone formulation were significantly higher than that for Skelaxin (Table 4, Figure 4).

Table 4
Pharmacokinetic Parameters – PP99-642

Parameter	Metaxalone BB5800040 Mean (CV%)	Skelaxin GS639A Mean (CV%)	Ratio		
			Mean	% CV	Range
Cmax (Ln)Cmax 90% CI	1798 (37) 1669 202-266	777 (39) 721	250	43	119- 574
AUC (Ln)AUCt 90%CI	8138 7428 129-161	5672 5162	151	49	84-258
AUCinf (Ln)AUCinf 90% CI	8223 7518 124-154	5956 5453	144	45	81-228
Tmax	3	3			
T1/2	2	8			

Figure 4

Plasma Concentrations - P99-542



Summary

The in-vitro dissolution of metaxalone Lot # BB5800047, a pharmaceutically equivalent formulation to Skelaxin was slightly slower than the in-vitro dissolution of Skelaxin Lot # GS639A, using the dissolution method for release. However, the in-vivo evaluation found metaxalone Lot # BB5800047 to have a higher C_{max} and AUC than Skelaxin Lot # GS639A. Therefore the in-vitro dissolution using the dissolution method for release was not predictive of in-vivo performance for the pharmaceutical equivalents evaluated in this study.

Evaluation of alternative dissolution methodologies

The in-vitro dissolution using the dissolution method for release (USP II, 75rpm, 1000ml water with 2% SLS) was not predictive of the in-vivo performance of Skelaxin and two pharmaceutically equivalent products (Lot # BB5800040 and BB5800047). Figures 5 and 6 summarise the in-vitro and in-vivo performance of these formulations.

The in-vitro and in-vivo performance of Skelaxin was similar for the two studies. Metaxalone Lot # BB5800040 was faster in-vitro than Skelaxin and showed a loss in bioavailability in vivo compared to Skelaxin. Metaxalone Lot # BB5800047 was slower in-vitro than Skelaxin and was superbioavailable in-vivo compared to Skelaxin.

Figure 5

Dissolution of 400mg tablets in USP II @ 75rpm, 1000ml 2% SLS in water (Release Data)

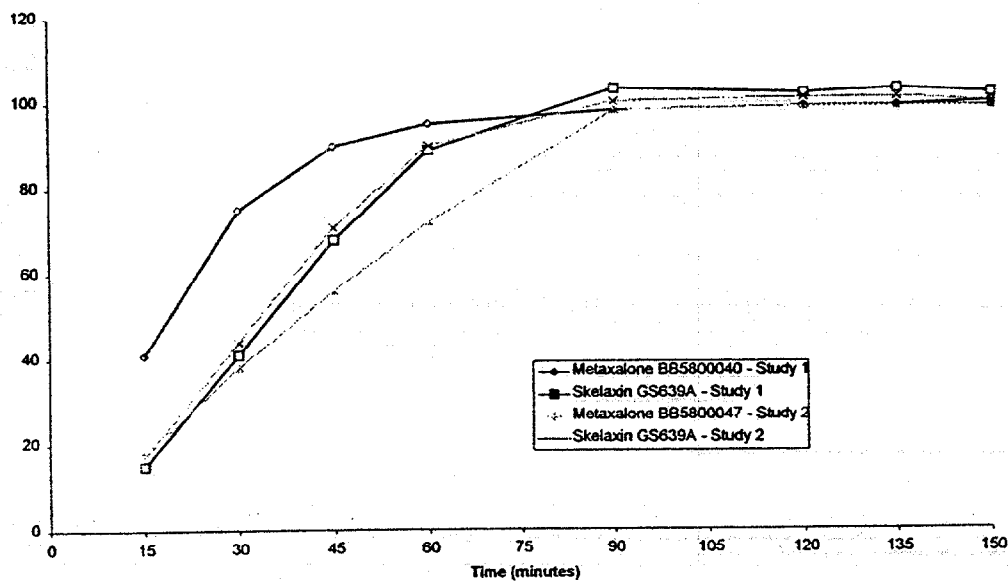
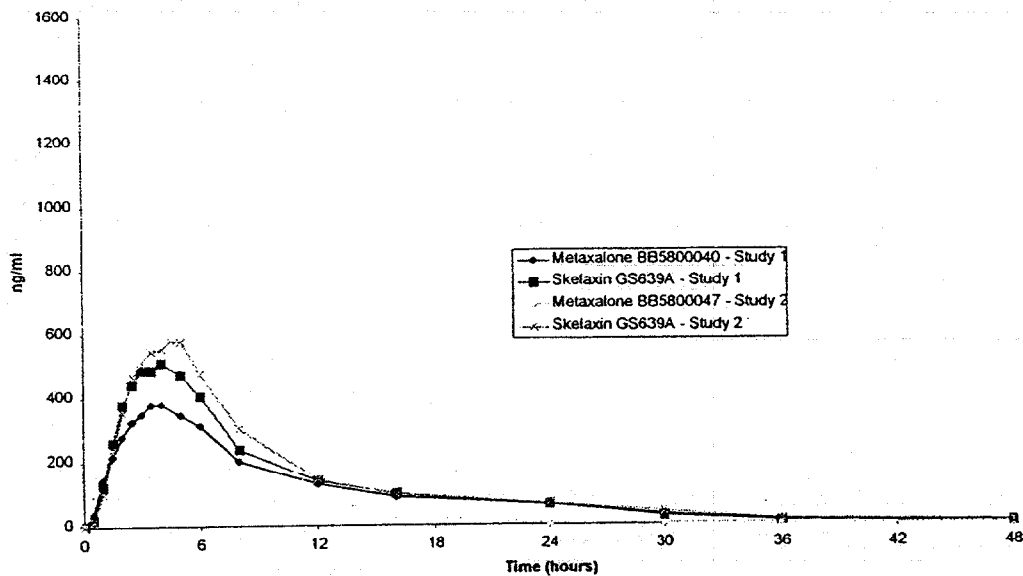


Figure 6

In-Vivo Data

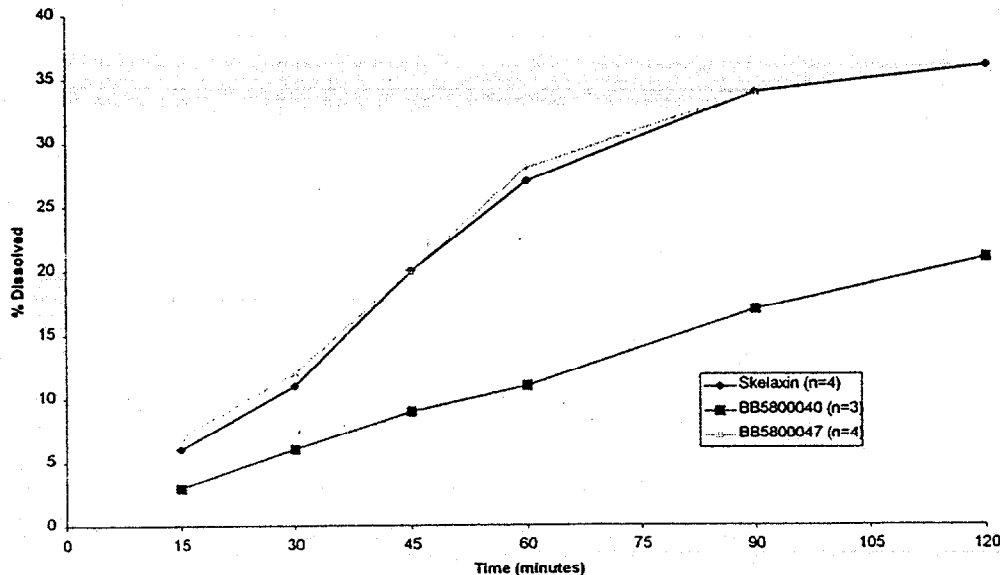


The in-vitro performance of Skelaxin and the pharmaceutically equivalent metaxalone formulations were evaluated using an alternative dissolution medium (500ml water with 0.25% SLS, paddles at 25rpm using peak vessels) to determine if this dissolution system might be capable of predicting the in-vivo performance of these formulations. This method was chosen as it was considered less severe in terms of agitation and surfactant concentration and the volume of media was lower, which might better reflect in-vivo conditions.

Figures 7 summarises the dissolution of the three formulations using this method. Approximately three units were evaluated in each case.

Figure 7

500ml water with 0.25% SLS, paddles at 25rpm using peak vessels



Summary

This data shows that there is a significant impact of both agitation and surfactant concentration on the release of metaxalone from Skelaxin and the pharmaceutically equivalent metaxalone formulations. The impact of the dissolution conditions affects the three formulations differently. Lot # BB5800047 was found to be comparable to Skelaxin which is not the case in-vivo, while the dissolution of Lot# BB5800040 better reflected the in-vivo performance.

Conclusions

The data presented indicates that in-vitro dissolution using standard dissolution methods is not predictive of in-vivo performance for pharmaceutically equivalent formulations of Skelaxin, the slowly dissolving IR solid dosage form of the poorly soluble drug metaxalone. In addition, altering the dissolution conditions alters the comparative performance of these formulations. As dissolution appears to be dependent on formulation or process parameters, dissolution conditions that achieve an in vivo / in vitro correlation for these formulations, might not be appropriate for predicting the in-vivo performance of alternative formulations. This data therefore provides compelling evidence that in-vitro dissolution cannot be used as a surrogate of in-vivo performance for pharmaceutical equivalents of Skelaxin.

**Illinois Department of
Public
Health**

George H. Ryan, Governor - John R. Lumpkin, M.D., M.P.H., Director

525-535 West Jefferson Street • Springfield, Illinois 62761-0001

March 22, 2001

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs
Carrick Laboratories
Élan Pharmaceutical Research Corporation
1300 Gould Drive
Gainesville, GA 30504

Dear Mr. Wiley:

Enclosed is a metaxalone biostudy submission received by the Department of Public Health in support of Zenith Goldline Pharmaceutical's petition for listing of their product in the Illinois Formulary for the Drug Product Selection Program.

Should your company have any comments relative to the bioequivalency of this product, please provide 10 copies of your remarks to this office no later than close of business on April 16, 2001.

If you have any questions on this matter, I may be reached at (217) 782-7532.

Sincerely,



Ronald W. Gottsch, R.Ph., M.S.
Manager, Drugs and Medical Devices Programs
Division of Food, Drugs and Dairies

APPLICATION FOR INCLUSION OF DRUG PRODUCT IN THE ILLINOIS FORMULARY

1. Name of manufacturer/application holder: Zenith Goldline Pharmaceuticals, Inc.	2. Date of application: 2/16/01
3. Mailing address of manufacturer/application holder: 140 Legrand Avenue Northvale, NJ 07647	4. Address of manufacturing site (if different): Zenith Laboratories Caribe, Inc. Cidra Industrial Park P.O. Box 11979 Cidra, Puerto Rico 00739
5. Name of contact person (for clarification of this application): Tracie A. Buranicz, Pharm.D.	6. Contact person's telephone number and e-mail address: (201) 767-1700 x 327 tracie_buranicz@lvax.com
7. Reference brand for which above is a substitute: Skelaxin® of Carrick Laboratories	8. Dosage form: Tablets
9. Generic name and strength(s) of drug product(s) submitted for inclusion in the <i>Illinois Formulary</i> for single ingredient items OR name and amount of each active ingredient: Metaxalone Tablets, 400 mg	
10. Does each batch of this drug product conform with official standards prior to being marketed? ____ Yes ____ No	11. Date last inspected by FDA for CGMP compliance: 6/30/00
12. Date of drug product's FDA approval: Not approved at this time.	13. Is this drug product: Manufactured under an ANDA? ____ Yes ____ No Manufactured under the NDA? ____ Yes ____ No
14. Have bioequivalence studies been submitted to the FDA? ____ Yes ____ No If no, why not? See attached	15. Is this product subject to a bioequivalence waiver? ____ Yes ____ No If yes, please provide a copy.
16. Has this drug product been involved in any litigation, including patent suits, in the last two years? ____ Yes ____ No If yes, attach particulars	17. Does the name of the manufacturer appear on all distributors' labels? ____ Yes ____ No
18. Is this product currently available to Illinois pharmacies? ____ Yes ____ No If no, when will it be launched? Approval is expected near the end of 2001.	
19. National Drug Code: 0172-6250-xx	20. Usual cost to pharmacies (AWP/100 or specify) Not available at this time.

I agree to inform the Illinois Department of Public Health in writing of any changes in the information listed in this application within 30 days of such change, and do certify that the information submitted is, to the best of my knowledge, correct and that this product is not in violation of either Federal or State Law.

Tracie A. Buranicz
Signature

Tracie A. Buranicz, Pharm.D.
Printed name

Regulatory Affairs Associate
Title

**Zenith Goldline**
PHARMACEUTICALSMetaxalone
Abbreviated New 1**SECTION VI****Bioavailability/Bioe****4. Request for Waiver of *In Vivo* Study:**

A Request for Waiver of *In Vivo* study is not applicable.

NOTE: Reference is made to a telephone correspondence between Zenith Goldline and Ms. Krista Scardina of the Division of Bioequivalence on November 9, 2000. The Agency informed Zenith Goldline that Metaxalone Tablets, 400 mg are designated as a DESI drug and that *in-vivo* bioequivalency studies are not required for an abbreviated new drug application. Accordingly, appropriate *in-vitro* bioequivalence studies demonstrating that the proposed drug product is bioequivalent to the reference listed drug are provided in Section VI.S. of this application.

**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method: USP <711>
Apparatus: 2 (paddles)
RPM: 75
Medium: 2% Sodium Lauryl Sulfate
Volume: 900 mL at 37°C
Tolerance (Q): Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$
(Metaxalone) is dissolved in 120 minutes

Product	Manufacturer	Lot Number	Expiry Date
Metaxalone Tablets, 400 mg	Zenith Goldline Pharmaceuticals	ND-637	08/2002*
Skelaxin® Tablets, 400 mg	Carrick Laboratories	GS779A	05/2002

* Proposed expiry date.

Comparative Assay and Content Uniformity Data are also provided.

NOTE: Supporting dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product using various media and paddle speeds are also provided in the following pages.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2 (paddles), 75 RPM, 900 mL, 2% Sodium Lauryl Sulfate, 120 minutes

TOLERANCE: NLT 60%(Q) of the labeled amount of $C_{12}H_{11}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 08/22/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 08/26/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	10	22	32	45	60	82	99
2	10	23	34	48	63	85	97
3	10	21	30	43	58	79	95
4	10	21	32	45	59	81	96
5	11	23	34	48	63	85	98
6	11	23	34	47	61	83	97
7	12	23	34	49	64	85	98
8	12	24	35	49	62	86	98
9	11	23	34	48	63	85	97
10	10	20	30	45	59	78	93
11	11	23	34	49	63	84	98
12	11	23	34	48	63	85	98
MEAN	11%	22%	33%	47%	62%	83%	97%
RANGE	10-12%	20-24%	30-35%	43-49%	58-64%	78-86%	93-99%
SD	7.0%	5.2%	5.1%	4.4%	3.3%	3.2%	1.7%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	8	26	45	68	91	102	103
2	7	22	41	66	87	100	101
3	10	28	48	75	93	100	101
4	6	18	33	58	80	99	101
5	10	25	43	69	88	98	98
6	8	23	41	66	86	101	102
7	9	25	44	70	89	100	101
8	10	28	45	68	87	99	101
9	10	28	49	75	82	98	100
10	10	29	48	74	81	99	100
11	10	28	48	74	93	102	102
12	10	27	48	78	82	101	101
MEAN	8%	25%	45%	70%	88%	100%	101%
RANGE	6-10%	18-29%	33-49%	58-75%	80-93%	98-102%	98-103%
SD	15.2%	12.7%	10.8%	7.0%	4.1%	1.3%	1.2%

This is the transcription of the laboratory records.

Transcription checked by: Debbie D. Crater DATE: 11/13/2000

0054

**COMPARISON STUDY
FOR ASSAY AND CONTENT UNIFORMITY
FOR METAXALONE TABLETS, 400 MG**

ZENITH'S PRODUCT:

Metaxalone Tablets, 400 MG
Lot # ND-637
Tentative Exp. Date: 8/2002
Test Date: 08/22/00
Method: MTX-LC-A-1

REFERENCE PRODUCT:

Skelaxin (Metaxalone) Tablets, 400 MG
Lot #: GS778A
Exp. Date: 5/2002
Test Date: 08/29/00
Method: MTX-LC-A-1

Metaxalone:					
Assay 1 = 99.0%					
Assay 2 = 99.1%					
Assay 3 = 99.1%					
Content Uniformity (in percent) by Weight Variation					
1	98.7	11	99.1	21	99.5
2	99.3	12	99.1	22	98.9
3	99.1	13	98.8	23	98.7
4	99.5	14	99.1	24	98.6
5	98.9	15	99.1	25	99.1
6	98.7	16	99.1	26	99.7
7	98.9	17	99.0	27	99.9
8	98.7	18	98.7	28	99.3
9	99.5	19	98.6	29	99.2
10	99.7	20	99.3	30	99.2
Mean = 99.1%					
Range = 98.6% - 99.9%					
RSD = 0.35%					

Skelaxin:	
Assay 1 = 98.5%	
Assay 2 = 98.2%	
Content Uniformity (in percent) by Weight Variation	
1	99.0
2	99.3
3	95.9
4	99.8
5	99.4
6	98.4
7	100.8
8	100.6
9	98.5
10	98.6
Mean = 99.0%	
Range = 95.9% - 100.8%	
RSD = 1.4%	

This is the transcript of the laboratory records.

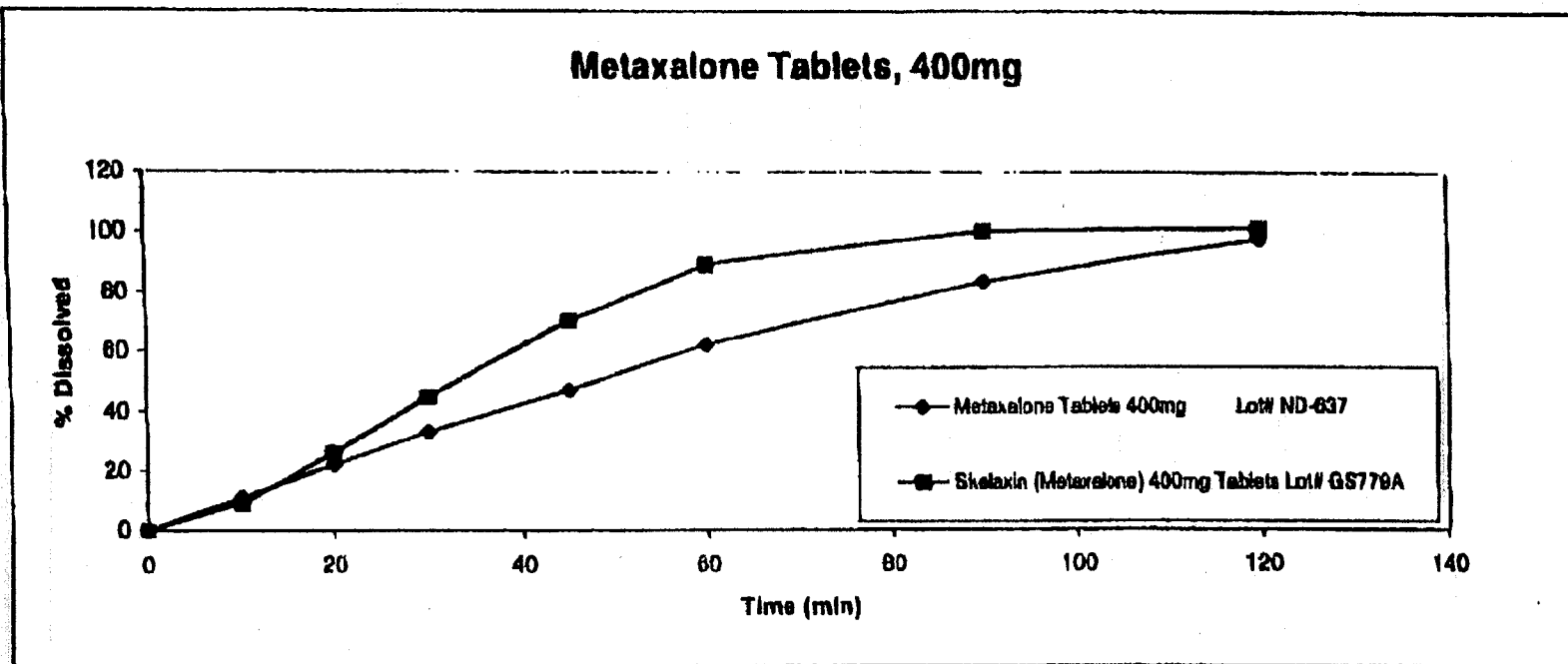
Transcription checked by: Deirdre J. Castro

Date: 11/9/2000

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG

USP Apparatus 2, 75 RPM, 900 mL, 2% Sodium Lauryl Sulfate, 120 minutes

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	11	9
20	22	26
30	33	45
45	47	70
60	62	89
90	83	100
120	97	101



0056

**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	2 (paddles)
RPM:	50
Medium:	Water at 37°C
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2, 50 RPM, 900 mL water at 37°C

TOLERANCE: NLT 60%(Q) of the labeled amount of $C_{12}H_{15}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 11/01/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/12/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	1	1	1	2	2	3	4
2	1	1	1	2	2	4	4
3	1	1	1	2	2	3	4
4	1	1	1	2	3	4	6
5	1	1	1	2	2	3	4
6	1	1	1	1	2	3	4
MEAN	1	1	1	2	2	3	4
RANGE	1	1	1	1-2	2-3	3-4	4-6
RSD	0.0%	0.0%	0.0%	22.3%	18.8%	16.5%	9.8%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	2	6	11	18	23	34	38
2	3	7	13	20	28	34	39
3	3	7	13	20	26	34	38
4	2	6	12	18	26	34	39
5	2	7	12	20	26	34	39
6	2	6	12	19	26	34	38
MEAN	2	7	12	18	26	34	38
RANGE	2-3	6-7	11-13	18-20	23-28	34-34	38-39
RSD	22.1%	8.4%	8.2%	4.2%	4.0%	0.0%	1.4%

This is the transcription of the laboratory records.

Transcription checked by:

Rebecca J. Castro

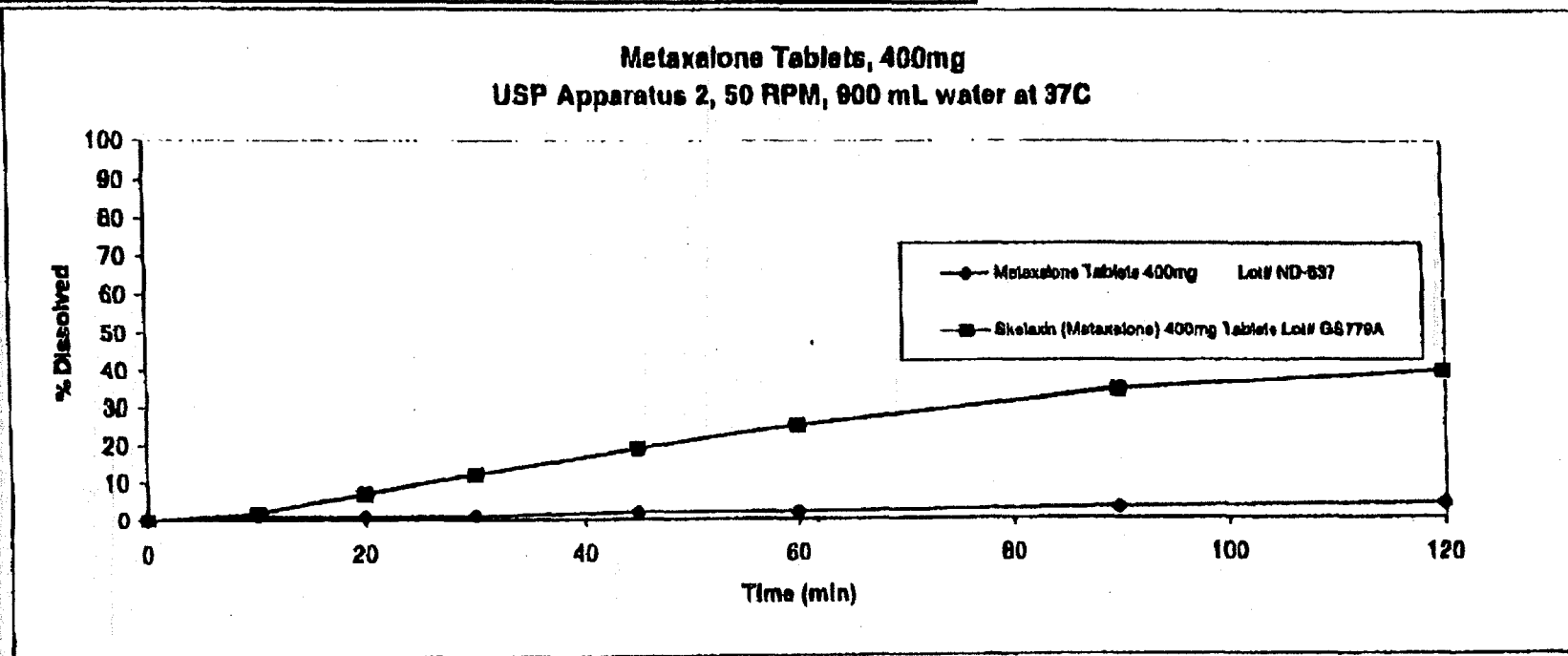
DATE:

11/20/2000

0056

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG
 USP Apparatus 2, 50 RPM, 900 mL, of Water at 37C

Time (min)	Metaxalone Tablets 400mg Lot# ND-837	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	1	2
20	1	7
30	1	12
45	2	19
60	2	25
90	3	34
120	4	39



0059

**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	2 (paddles)
RPM:	50
Medium:	Simulated Intestinal Fluid pH 6.8
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2 50 RPM, 900 mL of Sim. Intestinal Fluid pH 6.8

TOLERANCE: NLT 60% (Q) of the labeled amount of $C_{12}H_{15}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 11/02/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/12/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10'	20'	30'	45'	60'	90'	120'
1	2	5	8	13	19	30	43
2	1	5	7	13	18	30	43
3	2	5	7	14	21	30	40
4	2	6	8	14	21	33	45
5	2	6	8	12	17	28	40
6	2	6	8	14	21	33	46
MEAN	2	5	8	13	20	31	43
RANGE	1-2	5-6	7-8	12-14	17-21	28-33	40-48
RSD	22.3%	9.7%	6.7%	6.1%	9.0%	6.4%	5.8%

(PERCENT DISSOLVED IN MINUTES)

NO.	10'	20'	30'	45'	60'	90'	120'
1	1	3	8	9	12	18	25
2	1	3	7	12	17	29	38
3	1	3	7	10	15	25	34
4	1	3	6	9	13	23	32
5	2	4	8	12	17	28	35
6	1	3	6	10	14	24	33
MEAN	1	3	7	10	15	25	33
RANGE	1-2	3-4	6-8	9-12	12-17	18-29	25-38
RSD	35.0%	12.9%	12.2%	12.2%	14.1%	16.1%	12.1%

0061 This is the transcription of the laboratory records.

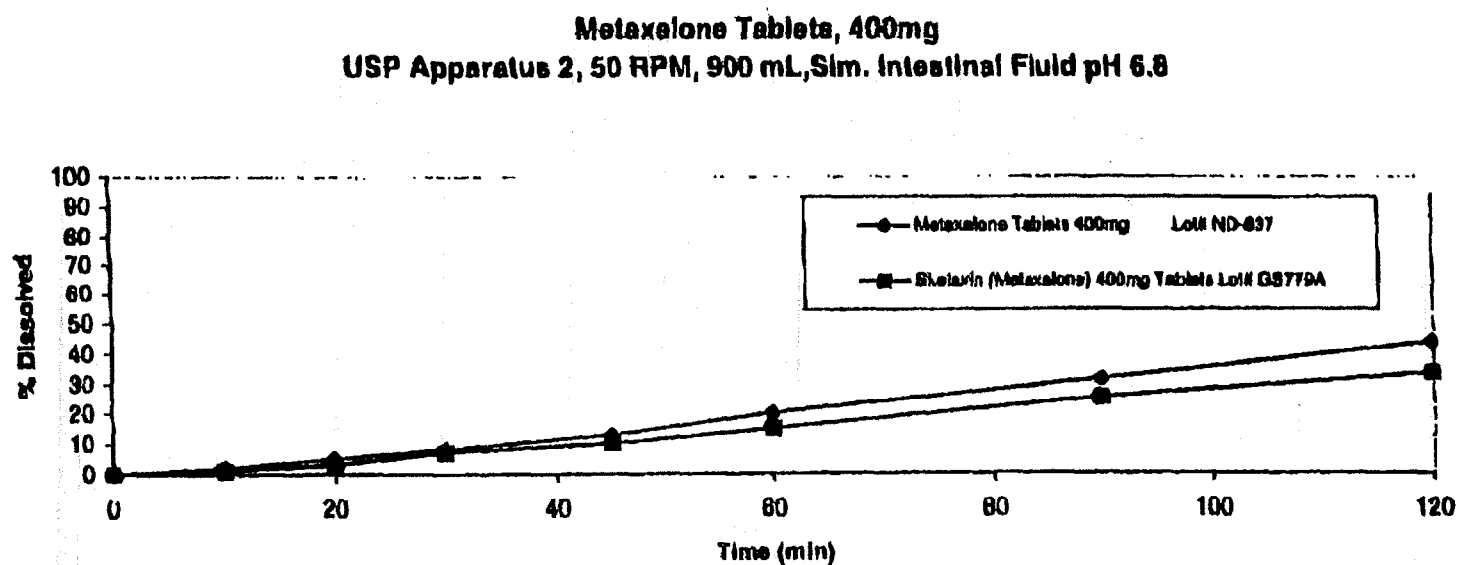
Transcription checked by: Annex G. Castro

DATE: 11/20/2000

COMPARATIVE DISSOLUTION STUDIES **METAXALONE TABLETS, 400 MG**

USP Apparatus 2, 50 RPM, 900 mL, Sim. Intestinal Fluid pH 6.8

Time (min)	Metaxalone Tablets 400mg Lot# ND-837	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	2	1
20	5	3
30	8	7
45	13	10
60	20	15
90	31	25
120	43	33



**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	2 (paddles)
RPM:	50
Medium:	Simulated Gastric Fluid pH 1.2
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2, 50 RPM, 900 ml of Sim. Gastric Fluid pH 1.2

TOLERANCE: NLT 60%(Q) of the labeled amount of $C_{12}H_{15}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 11/01/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/08/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	0	1	1	2	2	4	5
2	0	1	1	2	2	4	8
3	0	1	1	2	2	4	5
4	1	2	4	7	10	15	21
5	0	1	1	2	2	3	5
6	0	1	1	2	2	3	5
MEAN	0	1	2	3	3	6	8
RANGE	0-1	1-2	1-4	2-7	2-10	3-15	5-21
RSD	244.9%	35.0%	81.6%	72.0%	98.0%	85.1%	82.5%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	0	0	1	0	1	1	2
2	0	0	1	0	1	2	2
3	0	0	0	0	1	1	2
4	0	0	1	0	1	2	2
5	0	0	1	0	1	2	2
6	0	0	1	0	1	2	2
MEAN	0	0	1	0	1	2	2
RANGE	0	0	0-1	0	1	1-2	2-2
RSD	#DIV/0!	#DIV/0!	49.0%	#DIV/0!	0.0%	81.0%	0.0%

This is the transcription of the laboratory records.

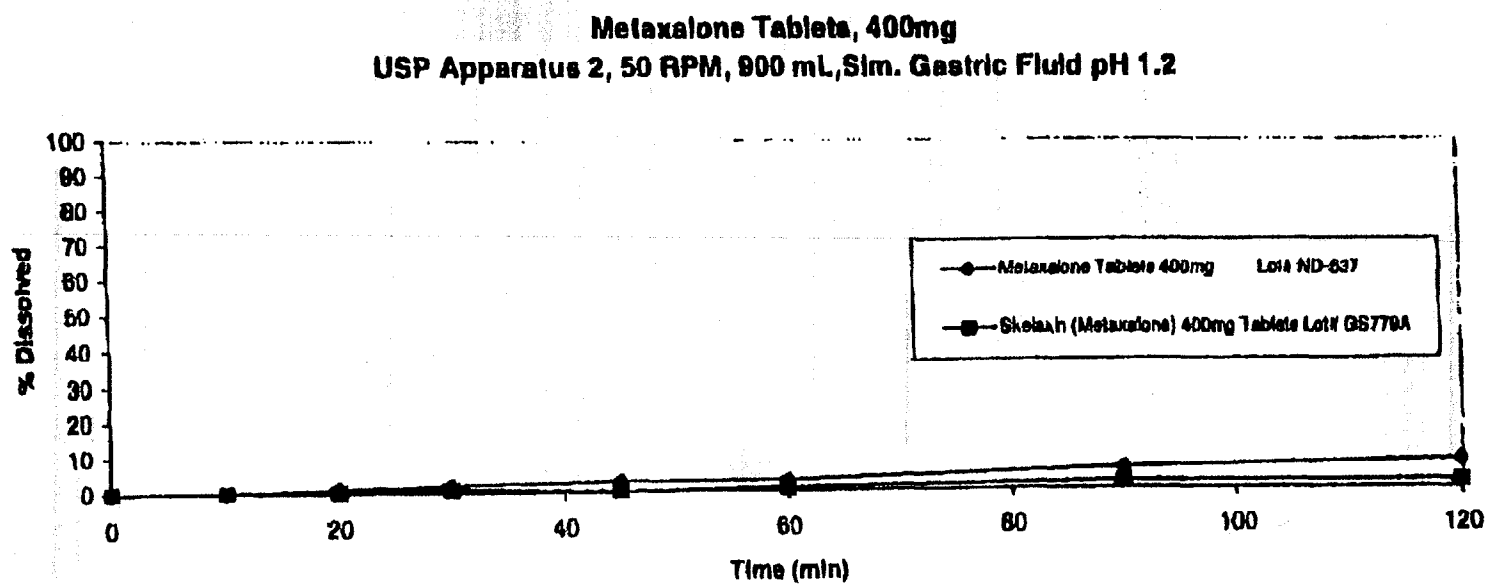
Transcription checked by: Renee R. Castro DATE: 11/20/2000

PUUJ

COMPARATIVE DISSOLUTION STUDIES **METAXALONE TABLETS, 400 MG**

USP Apparatus 2, 50 RPM, 900 mL, Sim. Gastric Fluid pH 1.2

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	0	0
20	1	0
30	2	1
45	3	0
60	3	1
90	6	2
120	8	2



0065

**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	2 (paddles)
RPM:	75
Medium:	Water at 37°C
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2, 75 RPM, 900 mL of Water @ 37°C

TOLERANCE: NLT 60% (Q) of the labeled amount of $C_{17}H_{19}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 10/29/2000

REFERENCE PRODUCT:

SKELEXIN (METAXALONE) 400 MG TABLETS

Lot #: GS778A

Exp. Date: 05/2002

Test Date: 10/17/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	1	2	2	3	4	5	7
2	1	2	3	4	5	8	8
3	1	2	3	4	5	7	9
4	2	3	4	5	8	9	10
5	1	2	3	4	5	7	8
6	1	2	2	3	4	8	7
MEAN	1	2	3	4	5	7	8
RANGE	1-2	2-3	2-4	3-5	4-8	5-9	7-10
RSD	35.0%	18.8%	26.6%	19.6%	15.6%	20.6%	14.5%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	4	12	21	33	42	53	58
2	4	13	22	35	44	55	61
3	4	12	21	34	43	54	59
4	5	14	23	35	43	54	59
5	5	14	24	37	44	55	60
6	5	14	24	38	44	54	59
7	4	15	22	34	44	56	61
8	4	15	22	33	42	52	59
9	4	15	21	33	43	52	59
10	4	14	20	32	41	52	57
11	5	18	23	35	45	55	60
12	4	15	21	32	42	52	59
MEAN	4	14	22	34	43	54	59
RANGE	4-5	12-18	20-24	32-37	41-45	52-55	57-61
RSD	11.4%	8.8%	6.8%	4.8%	2.7%	2.4%	2.1%

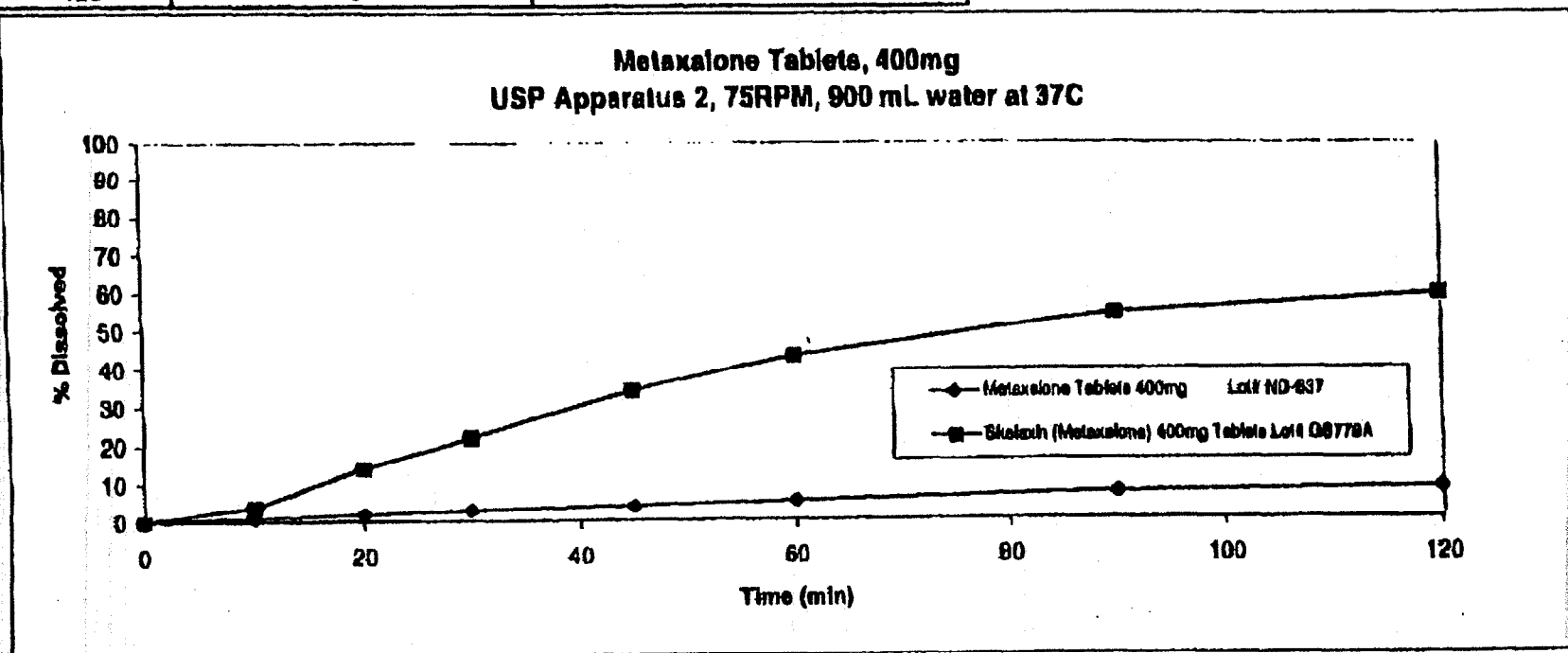
This is the transcription of the laboratory records.

Transcription checked by: Kevin J. Castro

DATE: 11/17/2000

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG
 USP Apparatus 2, 75 RPM, 900 mL, of Water at 37C

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	1	4
20	2	14
30	3	22
45	4	34
60	5	43
90	7	54
120	8	59



8900

**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence**5. **In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	2 (paddles)
RPM:	75
Medium:	Simulated Intestinal Fluid pH 6.8
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2, 75 RPM, 900 mL of Sim. Intestinal Fluid pH 6.8

TOLERANCE: NLT 60% (Q) of the labeled amount of $C_{12}H_{15}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 10/29/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/18/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	40	60	90	120
1	4	10	18	31	38	54	60
2	3	9	16	28	36	50	58
3	3	7	13	26	32	48	56
4	3	7	12	23	31	48	57
5	3	7	12	23	31	47	56
6	3	9	16	28	38	50	59
MEAN	3	8	15	26	34	50	58
RANGE	3-4	7-10	12-18	23-31	31-38	47-54	56-60
SD	12.8%	16.8%	17.9%	12.2%	9.7%	6.1%	2.3%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	40	60	90	120
1	2	7	12	22	31	45	62
2	2	7	12	21	30	46	63
3	3	7	13	23	32	48	62
4	3	7	12	22	31	48	62
5	3	8	14	24	34	48	66
6	3	7	13	23	32	46	61
7	3	8	15	23	32	48	66
8	3	8	14	22	30	46	62
9	3	8	15	23	31	46	63
10	3	8	14	22	31	46	63
11	4	10	17	26	36	48	66
12	3	8	15	22	31	46	62
MEAN	3	8	14	23	32	46	62
RANGE	2-4	7-10	12-17	21-26	30-36	45-48	61-66
SD	17.7%	11.2%	10.4%	4.7%	4.7%	2.8%	2.6%

This is the transcription of the laboratory records.

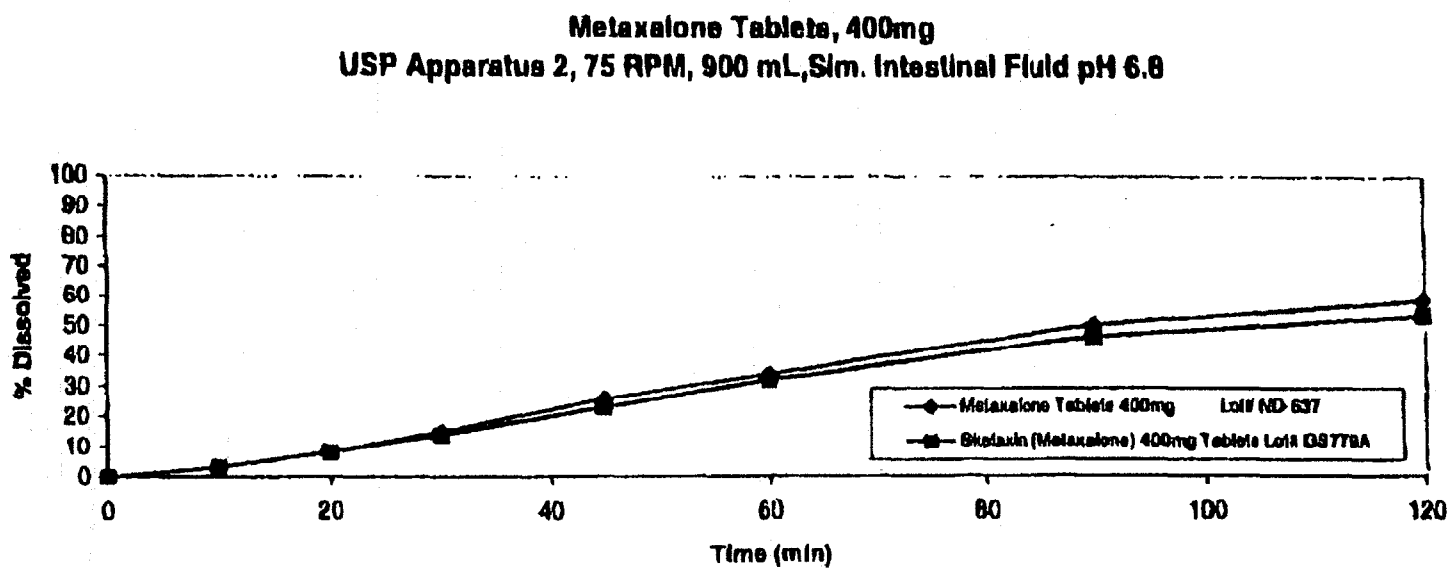
Transcription checked by: Quinta J. Castro

DATE: 11/17/2000

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG

USP Apparatus 2, 75 RPM, 900 mL, Sim. Intestinal Fluid pH 6.8

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	3	3
20	8	8
30	15	14
45	26	23
60	34	32
90	50	48
120	58	53



0071

**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.S.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	2 (paddles)
RPM:	75
Medium:	Simulated Gastric Fluid pH 1.2
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 2, 75 RPM, 900 ml. of Sim. Gastric Fluid pH 1.2

TOLERANCE: NLT 60% (Q) of the labeled amount of $C_{12}H_{15}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 10/29/2000

REFERENCE PRODUCT:

SKELEXIN (METAXALONE) 400 MG TABLETS

Lot #: GS77BA

Exp. Date: 05/2002

Test Date: 10/18/2000

(PERCENT DISSOLVED IN MINUTES)

No.	10	20	30	45	60	90	120
1	1	1	2	3	5	8	10
2	1	2	3	5	8	12	15
3	1	2	2	4	6	12	14
4	1	2	2	4	5	8	10
5	1	2	3	5	7	15	21
6	1	1	2	4	5	8	11
MEAN	1	2	2	4	6	11	14
RANGE	1	1-2	2-3	3-5	5-8	8-15	10-21
NSD	0.0%	31.0%	22.1%	18.1%	21.1%	28.1%	31.3%

(PERCENT DISSOLVED IN MINUTES)

No.	10	20	30	45	60	90	120
1	0	0	1	1	1	2	2
2	0	0	1	1	1	2	2
3	0	0	1	1	1	2	2
4	0	0	1	1	1	2	2
5	0	0	1	1	1	2	2
6	0	0	1	1	1	2	2
7	0	0	1	1	1	2	2
8	0	0	1	1	1	2	2
9	0	0	1	1	1	2	2
10	0	0	1	1	1	2	2
11	0	0	1	1	1	2	2
12	0	0	1	1	1	2	2
MEAN	0	0	1	1	1	2	2
RANGE	0	0	1	1	1	2	2
NSD	#DIV/0!	#DIV/0!	0.0%	0.0%	0.0%	0.0%	0.0%

This is the transcription of the laboratory records.

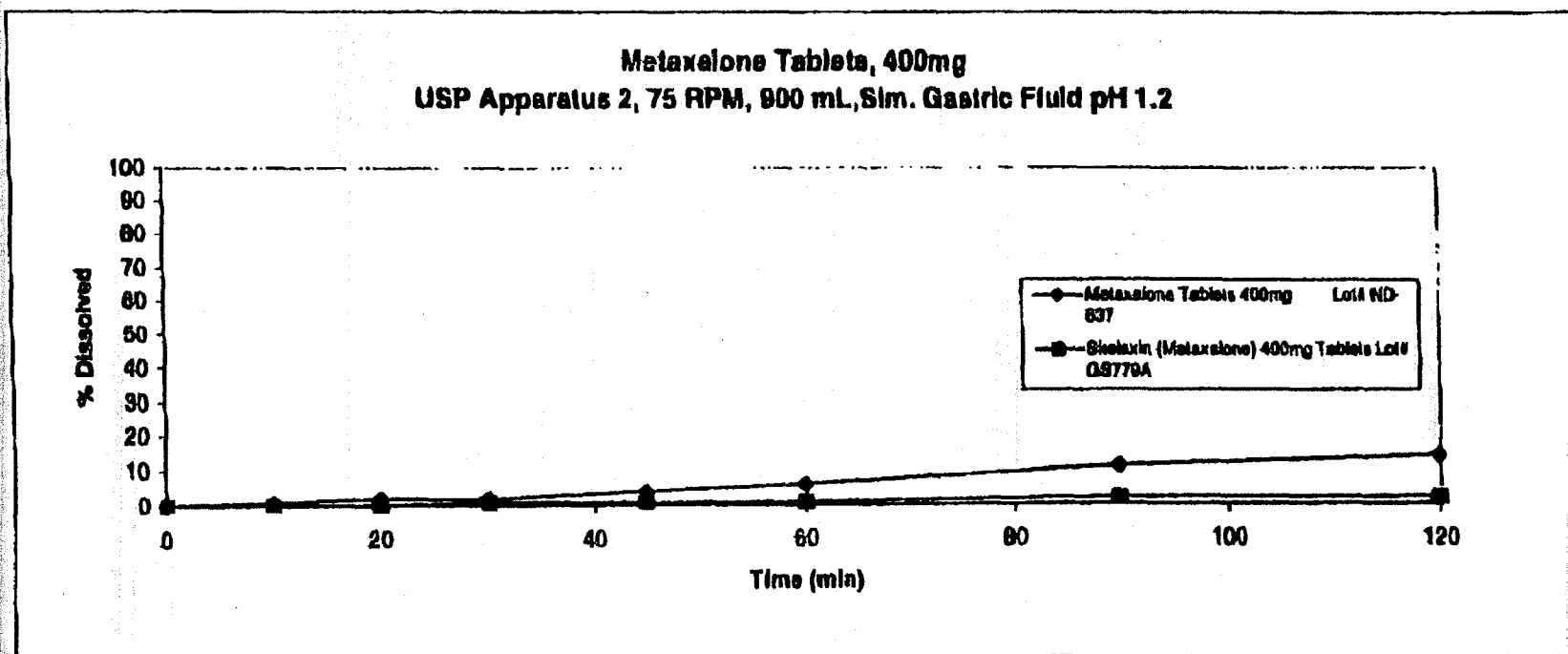
Transcription checked by: Rebecca B. Castro

DATE: 11/17/2000

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG

USP Apparatus 2, 75 RPM, 900 mL, Sim. Gastric Fluid pH 1.2

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	1	0
20	2	0
30	2	1
45	4	1
60	6	1
90	11	2
120	14	2



**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	1 (basket)
RPM:	100
Medium:	Water at 37°C
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 1, 100 RPM, 900 mL water at 37°C

TOLERANCE: NLT 60% (Q) of the labeled amount of $C_{12}H_{11}NO_3$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 11/02/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/04/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	1	1	7	3	4	5	6
2	1	1	2	3	4	5	6
3	1	1	2	3	4	5	6
4	1	2	2	3	4	6	7
5	1	1	2	2	3	4	6
6	1	1	2	3	3	5	6
MEAN	1	1	2	3	4	5	6
RANGE	1	1-2	2	2-3	3-4	4-6	5-7
RSD	0.0%	35.0%	0.0%	14.4%	14.1%	12.5%	10.5%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	5	13	18	24	29	37	42
2	5	12	17	23	28	35	40
3	5	12	16	23	27	35	41
4	3	8	13	20	26	35	40
5	5	12	17	23	27	35	41
6	6	13	18	23	27	32	37
MEAN	5	12	17	23	27	35	40
RANGE	3-6	8-13	13-18	20-24	26-29	32-37	37-42
RSD	20.3%	16.0%	11.3%	6.0%	3.8%	4.6%	4.3%

0076 This is the transcription of the laboratory records.

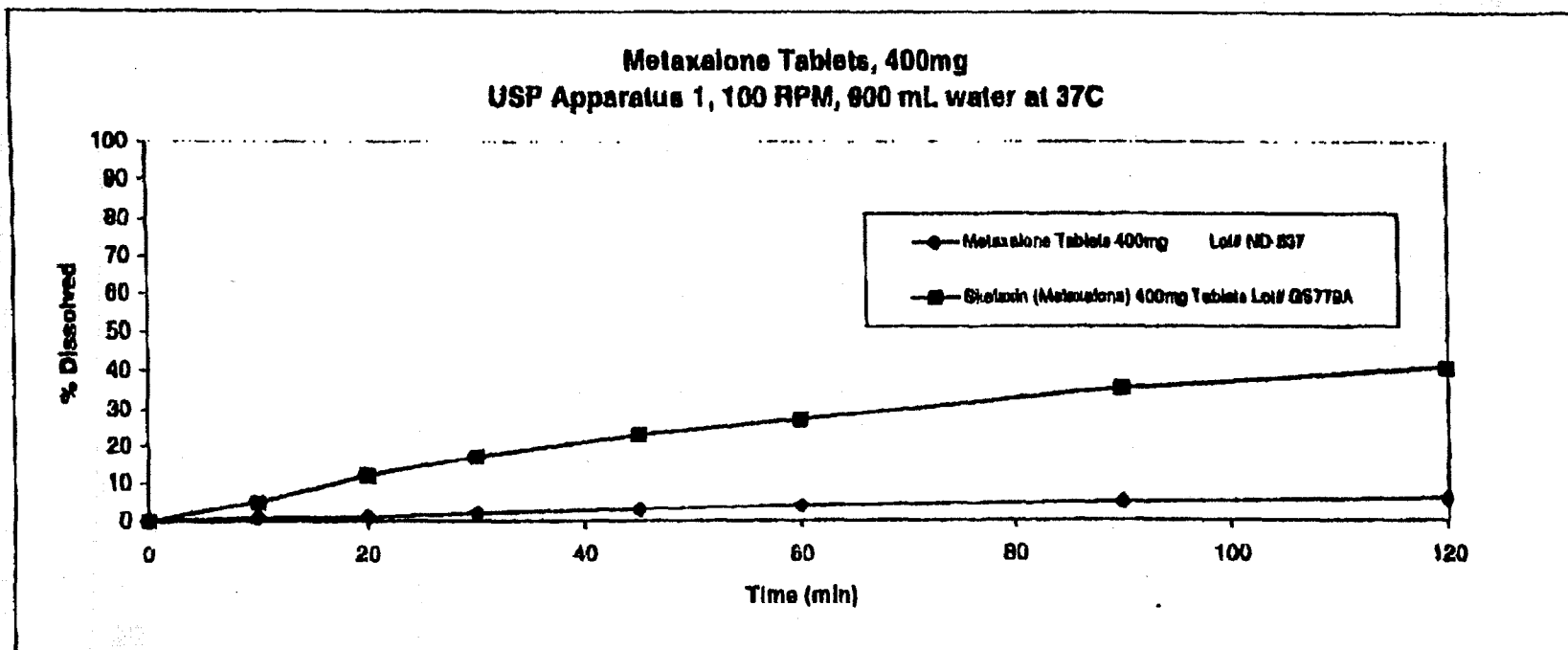
Transcription checked by: Deirdre A. Castro

DATE: 11/17/2002

COMPARATIVE DISSOLUTION STUDIES **METAXALONE TABLETS, 400 MG**

USP Apparatus 1, 100 RPM, 900 mL, of Water at 37C

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	1	5
20	1	12
30	2	17
45	3	23
60	4	27
90	5	35
120	6	40



**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****5. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.5.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	1 (basket)
RPM:	100
Medium:	Simulated Intestinal Fluid pH 6.8
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 1, 100 RPM, 900 mL Sim. Intestinal Fluid pH 6.8

TOLERANCE: NLT 60%(Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 11/02/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/10/2000

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	3	8	16	22	29	38	46
2	3	7	15	20	28	37	44
3	3	7	14	20	28	37	45
4	2	6	11	17	23	34	42
5	2	6	12	18	25	36	44
6	2	6	12	18	26	37	48
MEAN	3	6	13	19	26	37	45
RANGE	2-3	6-9	11-16	17-22	23-29	34-38	42-48
SD	21.9%	25.8%	14.7%	9.6%	7.5%	3.8%	4.4%

(PERCENT DISSOLVED IN MINUTES)

NO.	10	20	30	45	60	90	120
1	2	8	10	14	18	24	27
2	3	8	13	17	19	23	25
3	3	8	13	17	20	23	26
4	3	8	13	17	19	23	26
5	4	8	13	17	18	22	25
6	4	8	13	17	20	23	28
MEAN	3	8	13	17	19	23	26
RANGE	2-4	6-8	10-13	14-17	18-20	22-24	25-27
SD	23.6%	10.6%	9.8%	7.4%	3.8%	2.7%	3.2%

0079

This is the transcription of the laboratory records.

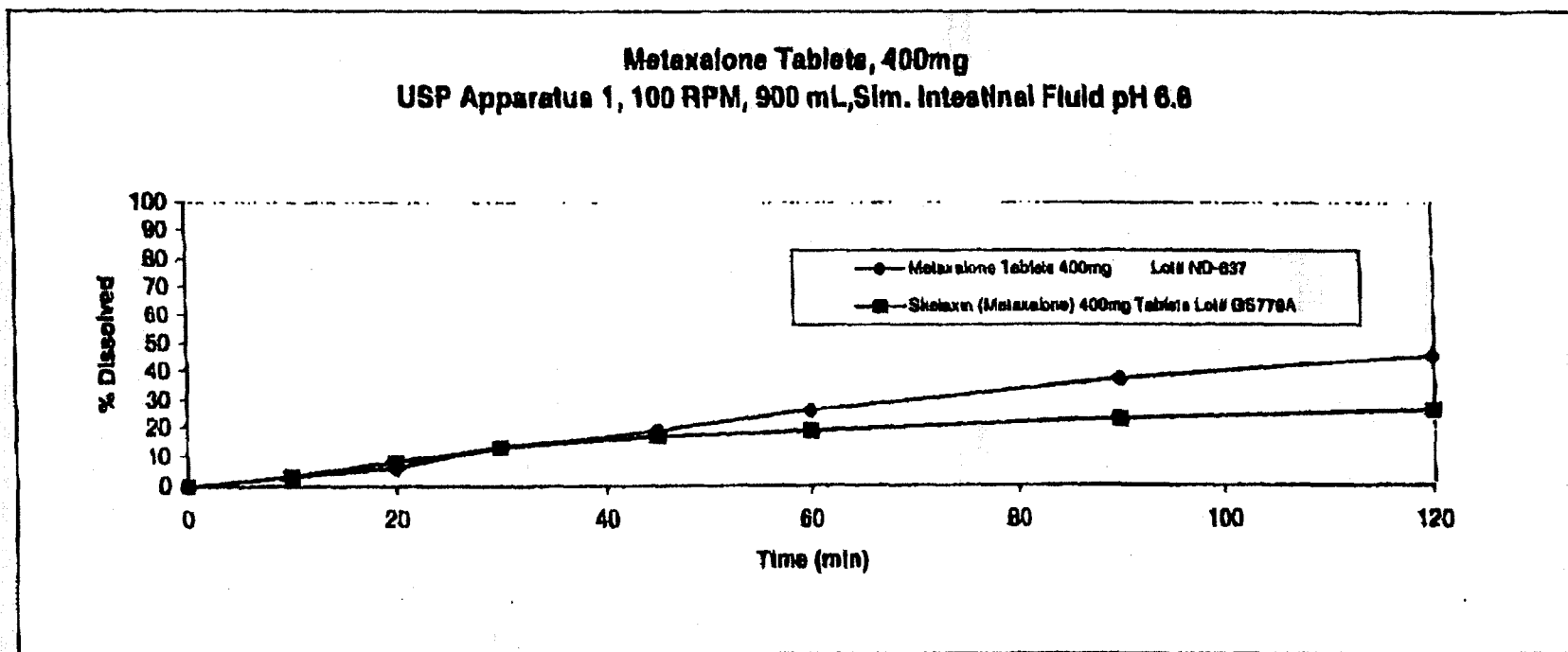
Transcription checked by: Reith J. Carter

DATE: 11/20/2000

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG

USP Apparatus 1, 100 RPM, 900 mL, Sim. Intestinal Fluid pH 6.8

Time (min)	Metaxalone Tablets 400mg Lot# ND-637	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	3	3
20	6	8
30	13	13
45	19	17
60	26	19
90	37	23
120	45	26



**Zenith Goldline**
PHARMACEUTICALS**Metaxalone Tablets, 400 mg**
Abbreviated New Drug Application**SECTION VI****Bioavailability/Bioequivalence****S. In Vitro Comparative Dissolution Data:**

Additional dissolution testing using various media and paddle speeds was done to support the original *in-vitro* comparative dissolution data presented in the beginning of this subsection (Section VI.S.). Comparative dissolution data for 12 dosage units of the test product versus 12 dosage units of the reference product, from the same lots used in the *in vivo* bioequivalence study, follows:

Dissolution Method:	USP <711>
Apparatus:	1 (basket)
RPM:	100
Medium:	Simulated Gastric Fluid pH 1.2
Volume:	900 mL
Tolerance (Q):	Not Less Than 60% (Q) of the labeled amount of $C_{12}H_{15}NO_3$ (Metaxalone) is dissolved in 120 minutes

NOTE: The bold type in the above table represents the difference between Zenith Goldline's established method and specification for dissolution testing and the testing performed as supporting *in-vitro* data.

COMPARATIVE DISSOLUTION STUDIES

Method of Analysis: MTX-LC-DIS-1

USP Apparatus 1, 100 RPM, 900 mL Sim. Gastric Fluid pH 1.2

TOLERANCE: NLT 60%(Q) of the labeled amount of $C_{11}H_{15}NO_2$ (Metaxalone) is dissolved in 120 minutes.

ZENITH'S PRODUCT:

METAXALONE TABLETS 400mg

Lot #: ND-637

Tentative Exp. Date: 08/2002

Test Date: 11/2/2000

REFERENCE PRODUCT:

SKELAXIN (METAXALONE) 400 MG TABLETS

Lot #: GS779A

Exp. Date: 05/2002

Test Date: 10/11/2000

(PERCENT DISSOLVED IN MINUTES)

TIME	10	20	30	45	60	90	120
1	1	1	2	3	3	6	8
2	1	1	2	2	3	6	8
3	1	1	2	2	3	4	6
4	1	1	2	3	4	7	10
5	1	1	2	3	4	6	9
6	1	1	2	3	3	6	8
MEAN	1	1	2	3	3	6	8
RANGE	1	1	2	2-3	3-4	4-7	6-10
SD	0.0%	0.0%	0.0%	19.4%	15.6%	18.2%	20.6%

(PERCENT DISSOLVED IN MINUTES)

TIME	10	20	30	45	60	90	120
1	0	1	1	1	2	2	3
2	0	1	1	1	2	2	3
3	0	1	1	1	2	2	3
4	0	1	1	1	1	2	3
5	0	1	1	1	1	2	3
6	0	1	1	1	2	2	3
MEAN	0	1	1	1	2	2	3
RANGE	0	1	1	1	1-2	2	3
SD	#DIV/0!	0.0%	0.0%	0.0%	31.0%	0.0%	0.0%

008130 This is the transcription of the laboratory records.

Transcription checked by:

Rebecca B. Castro

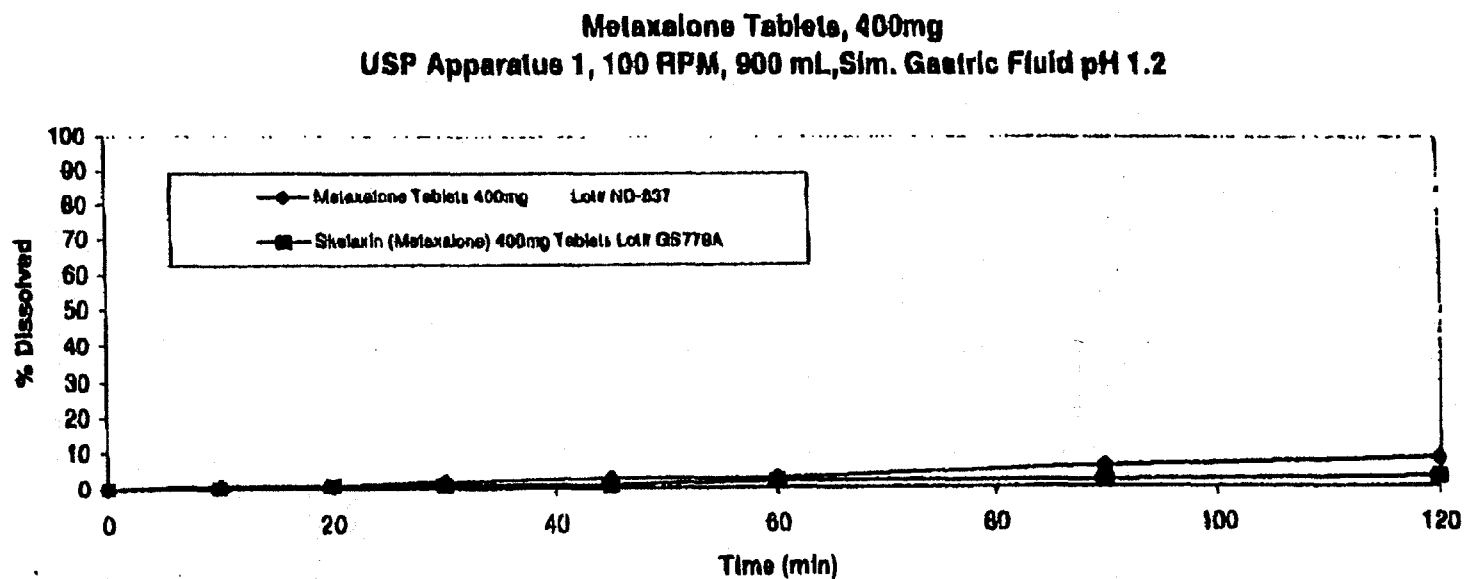
DATE:

11/20/2002

COMPARATIVE DISSOLUTION STUDIES
METAXALONE TABLETS, 400 MG

USP Apparatus 1, 100 RPM, 900 mL, Sim. Gastric Fluid pH 1.2

Time (min)	Metaxalone Tablets 400mg Lot# ND-837	Skelaxin (Metaxalone) 400mg Tablets Lot# GS779A
0	0	0
10	1	0
20	1	1
30	2	1
45	3	1
60	3	2
90	6	2
120	8	3



0083

TO - Brooks

DRUG UTILIZATION REVIEW COUNCIL
 New Jersey Department of Health and Senior Services
 Room 501, PO Box 360
 Market & Warren Streets, Health Agriculture Building
 Trenton, NJ 08625-0360
 Phone: (609) 292-4629 FAX: (609) 984-2218
www.state.nj.us/health/mgmt/drugutil.htm

Robert G. Kowalski, R.Ph.
 Acting Executive Director

April 11, 2001

To: All Drug Companies and Other Interested Parties

Subject: New Jersey Formulary Proposed Additions

Please be advised that the following proposed additions to the New Jersey Generic Formulary will be formally announced in the April 16, 2001, *New Jersey Register*.

The following drugs are listed alphabetically, in a format which represents the name of the substituted brand name drug (reference drug), the generic name of the drug product, the strength and the dosage delivery system of the drug product, and the names of the generic drug's manufacturers.

ACTIGALL, Ursodiol, 300 mg, Capsule, Novartis
 ALUPENT, Metaproterenol, 0.4%, 0.6%, Inhalation solution, Novex Pharma
 ANUSOL HC, Hydrocortisone acetate, 25 mg, Suppository, Able
 ATROVENT, Ipratropium bromide, 0.02%, Solution for Inhalation, Holopack, Novex Pharma
 BETAPACE, Sotalol HCl, 80 mg, 120 mg, 160 mg, 240 mg, Tablet, Impax
 BUSPAR, Buspirone HCl, 5 mg, 10 mg, 15 mg, Tablet, Geneva, Norton-Waterford Ltd. *SUSA*
 CLEOCIN, Clindamycin HCl, 150 mg, 300 mg, Capsule, Olin
 CREON 10, Lipase/amylase/protease, 10,000/33,200/37,500 USP Units, Capsule, Carlsbad Technology
 CREON 20, Lipase/amylase/protease, 20,000/66,400/75,000 USP Units, Capsule, Carlsbad Technology
 DAYPRO, Oxaprozin, 600 mg, Tablet, Eon, Mylan, Zenith Goldline
 DIDRONEL, Etidronate disodium, 200 mg, 400 mg, Tablet, Genpharm
 DILACOR XR, Diltiazem HCl, 120 mg, 180 mg, 240 mg, Capsule-Extended release, Biovail
 DILANTIN, Phenytoin sodium, 125 mg/5 ml, Suspension, UDL Labs
 DISALCID, Salicylate, 500 mg, 750 mg, Tablet, Able
 FLURESS, Fluorescein sodium/benoxinate HCl, 0.25%/0.4%, Solution-ophthalmic, Bausch & Lomb
 FOSAMAX, Alendronate sodium, 5 mg, 10 mg, 40 mg, Tablet, Zenith Goldline
 ✓ GLUCOPHAGE, Metformin HCl, 500 mg, 850 mg, Tablet, TEVA
 GLUCOPHAGE, Metformin HCl, 500 mg, 625 mg, 750 mg, 850 mg, 1000 mg, Tablet, Alphapharm, Andrx, Geneva, Genpharm
 ✓ GLUCOPHAGE, Metformin HCl, 500 mg, 625 mg, 750 mg, 850 mg, 1000 mg, Tablet, Zenith Goldline
 GLUCOTEOL, Glipizide, 5 mg, 10 mg, Tablet, TorPharm
 HYTONE, Hydrocortisone, 2.5%, Ointment, Thames
 INTAL, Cromolyn sodium, 20 mg/2 ml, Solution for nebulizer, Bausch & Lomb
 K-DUR, Potassium chloride, 10 mEq (750 mg), 20 mEq (1500 mg), Tablet Extended-release, Upsher-Smith
 LAC-HYDRIN, Ammonium lactate, 12%, Cream, Cobe Labs
 LEVBID, Hyoscyamine sulfate, 0.375 mg, Tablet Extended-release, Kramers-Urban
 LEVSINEX, L-hyoscyamine sulfate, 0.375 mg, Capsule Extended-release, Carlsbad Technology
 LOMOTIL, Diphenoxylate HCl/atropine sulfate, 2.5 mg/0.025 mg, Tablet, Able
 LUVOX, Fluvoxamine maleate, 25 mg, 50 mg, 100 mg, Tablet, TEVA
 ✓ LUVOX, Fluvoxamine maleate, 50 mg, 100 mg, Tablet, Genpharm
 MEVACOR, Lovastatin, 10 mg, 20 mg, 40 mg, Tablet, Purepac, TEVA
 MINOCIN, Minocycline HCl, 75 mg, Capsule, ESI/Lederle, Olin
 MS CONTIN, Morphine sulfate, 100 mg, Tablet Extended-release, Watson
 ✓ NAPRELAN, Naproxen sodium, 375 mg, 500 mg, Tablet Extended-release, Andrx
 NEURONTIN, Gabapentin, 100 mg, 300 mg, 400 mg, Capsule, Purepac
 NORLUTATE, Norethindrone acetate, 5 mg, Tablet, Barr
 OPTICROM, Cromolyn sodium, 4%, Solution ophthalmic, Novex Pharma

45/22/25

PANCREASE, Lipase/amylase/protease, 4,500/30,000/25,000 USP Units, Capsule, Carlsbad Technology
 PANCREASE MT 16, Lipase/amylase/protease, 16,000/48,000/48,000 USP Units, Capsule, Carlsbad Technology
 PANCREASE MT 20, Lipase/amylase/protease, 20,000/56,000/44,000 USP Units, Capsule, Carlsbad Technology
 PAXEL, Paroxetine HCl, 10 mg, 20 mg, 30 mg, 40 mg, Tablet, TorPharm
 ✓ PEPCID, Famotidine, 20 mg, 40 mg, Tablet, Carlsbad Technology, Cheminor Drugs Ltd., Eon, Geneva, Norton Waterford Ltd.
 ✓ PONTOCAINE, Tetracaine HCl, 0.5%, Solution-ophthalmic, Bausch & Lomb
 PROCARDIA XL, Nifedipine, 30 mg, Tablet Extended-release, Biovail
 PROLDIN DECANOATE, Fluphenazine decanoate, 25 mg/ml, Injection, Novex Pharma
 PROZAC, Fluoxetine HCl, 10 mg, Tablet, Alphapharm
 PROZAC, Fluoxetine HCl, 10 mg, 20 mg, Capsule, Geneva, Mylan
 RITALIN, Methylphenidate, 5 mg, 10 mg, 20 mg, Tablet, Able
 ROCALITROL, Calcitriol, 0.25 mcg, 0.5 mcg, Capsule, TEVA
 RONDEC DM DROPS (NEW FORMULA), Carbinoxamine maleate/dextromethorphan HBr/pseudoephedrine HCl, 2 mg/4 mg/
 15 mg/ml, Oral drops, Silark
 RONDEC DM SYRUP (NEW FORMULA), Brompheniramine maleate/dextromethorphan HBr/pseudoephedrine HCl, 4 mg/15
 mg/60 mg/5 ml, Syrup, Silark
 RONDEC DROPS (NEW FORMULA), Carbinoxamine maleate/dextromethorphan HBr/pseudoephedrine HCl, 2 mg/15 mg/ml, Oral drops, Silark
 RONDEC SYRUP (NEW FORMULA), Brompheniramine maleate/dextromethorphan HBr/pseudoephedrine HCl, 4 mg/60 mg/5 ml, Syrup, Silark
 SKELAXIN, Metaxalone, 400 mg, Tablet, Zenith
 STADOL NS, Butorphanol tartrate, 10 mg/ml, Masterec Dose Spray, Roxane
 TAMBOCOR, Flecainide acetate, 50 mg, 100 mg, 150 mg, Tablet, Alphapharm
 TAPAZOLE, Mechimazole, 5 mg, 10 mg, Tablet, Eon
 TORODOL, Ketorolac tromethamine, 15 mg/ml, 30 mg/ml, Injection, Novex Pharma
 ULTRAM, Tramadol HCl, 50 mg, Tablet, Alphapharm, TEVA
 ULTRASE MT 20, Lipase/amylase/protease, 20,000/65,000/65,000 USP Units, Capsule, Carlsbad Technology
 VASOTEC, Enalapril maleate, 2.5 mg, 5 mg, 10 mg, 20 mg, Tablets, Taro
 VIOKASE, Lipase/amylase/protease, 3,000/30,000/30,000 USP Units, Tablet, Carlsbad Technology
 ZEBETA, Bisoprolol fumarate, 5 mg, 10 mg, Tablet, TEVA
 ZESTRIL, Lisinopril, 2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, Tablet, Par
 ZOVIRAX, Acyclovir, 200 mg, Capsule, TorPharm
 ZOVIRAX, Acyclovir, 400 mg, 800 mg, Tablet, TorPharm

A Public Hearing will be held concerning these proposed additions on Monday May 14 2001, at 10:00 AM in Room 804,
 Health-Agriculture Building, Trenton, NJ 08625-0360. Comments on the proposal are to be submitted to Robert G. Kowalski no
 later than May 16, 2001, at the address on the letterhead. These products will be considered at the June 12, 2001, Drug Utilization
 Review Council meeting.

G7907



16 1191-21260

EDWARD M THMAITE ASSOC
 15 LOOKOUT POINT TRAIL
 TOTOWA NJ 07512

I

NEW JERSEY
 DEPARTMENT OF HEALTH
 AND SENIOR SERVICES
 DRUG UTILIZATION REVIEW COUNCIL
 P.O. BOX 360
 TRENTON, N.J. 08646-0360

